SUMMARY PANEL MEMORANDUM

TO: **General and Plastic Surgery Panel Members**

FROM: FDA's Inamed PMA Review Team

DATE: September 12, 2003

SUBJ: P020056 - Inamed Corporation
McGhan Silicone-Filled Breast Implants (Styles 10, 20, 40, 45, 110, 120, and 153)

INTRODUCTION: The primary elements of a PMA are the (1) device description, (2) preclinical data, (3) clinical data, (4) device reports, and (5) labeling. Below is a brief description of each of these sections.

1. **Device description** section provides a brief description of the device and identifies the styles under PMA review.

2. **Preclinical** sections include chemistry, toxicology, mechanical, retrieval study, and shelf life.

3. **Clinical** sections include:

   - Core Study - The Core Study is a 10-year prospective clinical study that collects safety (local complications) and effectiveness data on Inamed's silicone gel-filled breast implant Styles 40, 45, 110, 120, and 153 for augmentation, reconstruction, and revision indications. The Core Study does not include Style 10 or 20, which are two implant styles for which Inamed is seeking approval. This is the primary clinical data set for this PMA. **Please refer to Dr. Sahar Dawisha's memo entitled "Inamed Clinical Summary Memorandum" for a detailed review of these data.**

   - Adjunct Study - The Adjunct Study is an ongoing 5-year prospective clinical study that collects safety (local complications) data on implant Styles 10, 20, 40, 45, 110, 120, and 153 for reconstruction and revision patients. The Adjunct Study was established to make silicone gel-filled breast implants available for reconstruction and revision patients as per our 1992 determination that there was a public health need for these patients. **Please refer to Dr. Sahar Dawisha's memo entitled "Inamed Clinical Summary Memorandum" for a detailed review of these data.**

   - AR90 Study - The AR90 Study was a 5-year prospective study that collected safety (local complications) and effectiveness data on saline-filled and silicone gel-filled implants for augmentation and reconstruction. The final report of this study was submitted in 1999 in support of Inamed's saline-filled breast implant PMA. The AR90 Study involved silicone gel Styles 40, 80, 110, 120, 148, 153, and 246, as well as silicone/saline Styles 46, 156, 178, and 278. Of these 11 styles, only Styles 40, 110, 120, and 153 are included in this

PMA review (36% or 413/1136). The other styles are not being manufactured today. **Please refer to Dr. Sahar Dawisha's memo entitled "Inamed Clinical Summary Memorandum" for a detailed review of these data.**

- Statistical analysis for Core Study – This is the statistical summary for the Core Study.
- Literature review - The literature review provides retrospective data on safety issues that are not fully addressed through the data collected in the prospective clinical studies. The literature is not specific to Inamed's implants.
- SEER Study - The Surveillance Epidemiology End Results (SEER) Study review provides retrospective data on implant removal for breast implants. The SEER Study is not specific to Inamed's implants.
- Postapproval study plan - This is Inamed's plan for continued follow-up of the Core Study patients.

4. **Device report** sections include a general review of FDA's MedWatch information, a review of FDA's MAUDE information to supplement two safety issues primarily addressed by literature, and a review of Inamed's product experience report.

5. **Labeling** sections include an overview of the basic labeling of the device and a review of the focus group study protocol. The focus group study is designed to assess the adequacy of the patient labeling for this device.

Manufacturing information, another primary element of a PMA, will not be discussed in this Summary Panel Memorandum.

The purpose of this Summary Panel Memorandum is to provide you with a summary review of PMA elements except for the prospective clinical data (i.e., Core Study, Adjunct Study, and AR90 Study).

As noted above, please refer to Dr. Sahar Dawisha's memo entitled "Inamed Clinical Summary Memorandum" for a detailed review of the prospective clinical data. Along with a comprehensive review of the prospective clinical data, Dr. Dawisha's memo also includes a regulatory history of silicone gel breast implants and a brief summary of the significant literature published since 2000.

For additional information regarding FDA's recommendations for the types of preclinical and clinical data to submit in support of a breast implant PMA, please refer to "Guidance for Saline, Silicone Gel, and Alternative Breast Implants" dated 2/11/03 and available at http://www.fda.gov/cdrh/ode/guidance/1354.pdf.

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1. DEVICE DESCRIPTION

The McGhan Silicone-Filled Breast Implants are available in smooth and textured surfaces in round and shaped versions. The minimum shell thickness is 0.013" for the smooth implants and 0.018" for the textured implants. All styles are single lumen devices with the exception of Style 153. The Style 153 is a double lumen device consisting of an inner bladder within the outer lumen. Both the inner bladder and outer lumen are silicone filled. The inner bladder is located at the lower pole of the breast implant and its function is to maintain the curved profile of the style. All implants are dry heat sterilized.

The McGhan Silicone-Filled Breast Implants under PMA review are:

Style	Shape, Profile	Shell Surface	Volume (cc)
10	Round, Moderate Projection	Smooth	120-800
20	Round, Full Projection	Smooth	120-800
40	Round, Standard Projection	Smooth	80-560
45	Round, Full Projection	Smooth	120-800
110	Round, Moderate Projection	BIOCELL	90-510
120	Round, High Projection	BIOCELL	180-650
153	Shaped, Full Height, Full Projection	BIOCELL	360-720

The McGhan Silicone-Filled Breast Implant is composed of silicone gel encased in a silicone elastomer envelope (shell). The shell contains a patch, made from silicone elastomer, which covers the hole in the posterior shell that results when the shell is removed from the mandrel during manufacture. During manufacture, the gel is injected through the patch and the fill hole is sealed using a small amount of room temperature vulcanized (RTV) silicone adhesive. Thus, the primary components of the subject implants are the shell, patch, silicone gel filler, and silicone adhesive. Below is a detailed description of each of the primary components, including the materials.

The **shell** is manufactured using two different elastomers under high temperature vulcanization (HTV) conditions. [redacted] The shell consists of an inner and outer layer sandwiched around a "*barrier layer*" designed to impede the diffusion of components of the gel through the shell. All layers of the shell are produced using a [redacted] The barrier layer differs from the base layer in that it contains a [redacted]

The **patch** is manufactured from two types of silicone elastomers. [redacted]

The **silicone gel** consists of [redacted]

The RTV **silicone adhesive** used to seal the fill hole in the patch is [redacted]

[redacted]

Component	Material
Shell, middle (barrier) layer	[redacted]
Shell, inner/outer (base) layers	
Patch, outer layer	
Patch, inner (barrier) layer	
Silicone gel	
Silicone adhesive	

2. PRECLINICAL – CHEMISTRY DATA

Below is a review of the chemistry data.

Extent of Crosslinking

Shell and Patch Materials - The physical strength (tensile strength) and elasticity (elongation at failure) of the shell and patch materials is a result of the extent of crosslinking achieved during the vulcanization process. The physical properties of cured samples of all elastomer lots used for breast implant shells and patches are measured to ensure they meet or exceed pre-established material specifications prior to being released for use in the manufacture.

The results of this testing ensure the conformity of crosslink density across lots of implant shell and patch materials. In addition, the physical properties of the device shell, for three material lots under a variety of processing conditions, were measured during process validation testing. This testing ensures not only the consistency in the extent of crosslinking across material lots, but also ensures that the process used by Inamed to produce the implant shell is adequate to achieve a

crosslink density that assures the strength and elasticity of the implant shell meets or exceeds specifications. This testing demonstrated the extent of crosslinking of the elastomers used in the device shell is sufficient to assure all shells meet a specification of a minimum 3.0 lb break force and 380% elongation. Under the manufacturing conditions, the fumed amorphous silica that is used to reinforce the elastomer will stay in its amorphous form.

Gel Materials - [redacted] In addition, every batch of mixed gel is penetrometer-tested to ensure the crosslink density conforms to predetermined specifications.

[redacted] The gel material on FTIR analysis indicated the gel is made of siloxane material.

Volatiles

Analysis for volatiles present in gel was not necessary because the gel materials do not contain any organic solvents.

Analysis for volatiles present in the shell and patch material showed that the shell contained up to 279µg of 1,1,1 trichloroethane and 251µg of isopropyl alcohol.

Chemical Analyses of Low Molecular Weight Components (Extractables)

Finished sterilized devices were analyzed for extractables. The shell and the gel components of the device were separated and were subjected to chemical analysis. In addition, virgin shells, which had been patched and sterilized, but not yet gel-filled, were also extracted to provide information about the interaction between the gel and the shell materials. Table 1 below provides the amounts of various low molecular weight components present in the subject device. The techniques used to detect these components include solvent extraction followed by gas chromatography, using both a mass spectrometer (GC-MS) and a flame ionization detector (GC-FID), and by gel permeation chromatography (GPC). The concentration of various oligomers reported in Table 1 are the average values obtained from two extraction experiments.

The highest level of extracts was isolated using hexane as the extracting solvent. Everything detected in the extracts using the polar solvent (isopropanol) was also detected in the extracts using the non-polar solvent (hexane). Cyclic PDMS from $D_9 - D_{21}$ were detected and analyzed from extracts of both the shell and gel. Linear dimethylsiloxanes L_9 to L_{18} were detected in hexane extracts of the gel and shell that had been exposed to gel. The presence of linear siloxanes in the gel-exposed shell, which were not present in the virgin shell, indicates that components of the gel dissolve into the shell. Gravimetric analysis indicated that the gel dissolves in the shell at approximately 5% by weight of the shell. In addition, diphenyl containing siloxane components were found in the hexane extracts of the shell and gel. These diphenyl containing siloxanes are present in the shell as a result of the process used to produce the poly(dimethyldiphenyl)siloxane

polymer used in the shell elastomer formula. The presence of small amounts of diphenyl siloxane components in the gel indicated that the residuals in the shell migrate into the gel because no diphenyl containing polymers are used in the gel formulation.

The concentration of the smaller molecular weight oligomers is highly comparable to the concentration of oligomers present in the FDA-approved saline-filled breast implants.

Table 1: Concentrations of Low Molecular Weight Components Detected (in ppm by component weight).

Identification	Molecular Weight (amu)	Gel (ppm)	Implant Shell & Patch (ppm)	Virgin Shell & Patch (ppm)
D3	222	ND<146	ND<17	ND<7
D4	296	ND<69	ND<8	ND<3
D5	370	ND<6	ND<1	ND<1
D6	444	ND<6	ND<1	ND<1
D7	518	ND<6	ND<1	ND<1
D8	592	ND<8	ND<1	ND<1
D9	666	ND<8	6	ND<1
D10	740	ND<8	12	2
D11	814	11	21	9
D12	888	32	94	26
D13	962	64	62	65
D14	1036	237	186	209
D15	1110	366	278	285
D16	1184	491	351	317
D17	1258	593	432	328
D18	1332	729	527	342
D19	1406	678	601	0
D20	1480	735	605	212
D21	1554	668	474	129
L1	236	ND<63	ND<7	ND<3
L2	310	ND<8	ND<1	ND<1
L3	384	ND<8	ND<1	ND<1
L4	458	ND<10	ND<1	ND<1
L5	532	ND<8	ND<1	ND<1
L6	606	ND<7	ND<1	ND<1
L7	680	ND<8	2	4
L8	754	ND<8	2	ND<1
L9	828	ND<9	8	ND<1
L10	902	19	17	ND<1
L11	976	35	29	ND<1
L12	1050	63	49	ND<1
L13	1124	103	84	ND<1
L14	1198	132	108	ND<1
L15	1272	169	128	ND<1
L16	1346	183	106	ND<1
L17	1420	161	137	ND<1
L18	1494	177	128	ND<1
Diphenyl siloxanes	mixed	242	985	2762

Heavy Metal Analysis

Complete metal analyses were provided on the individual components of the device. Table 2 includes metals that are known to be potentially toxic. This analysis included virgin shell materials (i.e., not gel-exposed). The metal concentrations are comparable to the FDA-approved saline-filled breast implants.

Table 2: Concentrations of Metal Contents Detected (in ppm by component weight).

Metal	Atomic Weight (amu)	Virgin Shell (standard dispersion) (ppm)	Virgin Shell (barrier dispersion) (ppm)	Patch (ppm)	Gel (ppm)
Antimony	121.76	ND (<0.1)	ND (<0.1)	ND (<0.1)	ND (<0.1)
Arsenic	74.92	ND (<0.1)	ND (<0.1)	ND (<0.1)	ND (<0.1)
Barium	137.33	1	1	2	1
Beryllium	9.01	ND (<0.1)	ND (<0.1)	ND (<0.1)	ND (<0.1)
Cadmium	112.41	ND (<0.1)	ND (<0.1)	ND (<0.1)	ND (<0.1)
Calcium	40.08	ND (<10)	ND (<10)	ND (<10)	ND (<10)
Chromium	52.00	0.3	0.4	1.8	0.2
Cobalt	58.93	ND (<0.2)	ND (<0.2)	ND (<0.2)	ND (<0.2)
Copper	63.55	ND (<0.1)	ND (<0.1)	ND (<0.1)	ND (<0.1)
Iron	55.84	ND (<0.1)	0.2	8.7	1.2
Lead	207.19	ND (<0.2)	ND (<0.2)	ND (<0.2)	0.3
Magnesium	24.30	ND (<10)	ND (<10)	ND (<10)	ND (<10)
Manganese	54.94	ND (<0.05)	ND (<0.05)	0.15	ND (<0.05)
Mercury	200.59	ND (<1)	ND (<1)	ND (<1)	ND (<1)
Molybdenum	95.94	ND (<0.5)	ND (<0.5)	ND (<0.5)	ND (<0.5)
Nickel	58.69	ND (<0.2)	1	0.7	ND (<0.2)
Potassium	39.10	ND (<1)	8	1	ND (<1)
Selenium	78.96	ND (<0.1)	ND (<0.1)	ND (<0.1)	ND (<0.1)
Silver	107.87	ND (<0.1)	0.2	ND (<0.1)	ND (<0.1)
Sodium	22.99	ND (<10)	ND (<10)	ND (<10)	ND (<10)
Thallium	204.38	ND (<1)	ND (<1)	ND (<1)	ND (<1)
Vanadium	50.94	ND (<0.4)	ND (<0.4)	ND (<0.4)	ND (<0.4)
Zinc	63.40	0.12	ND (<0.05)	3.9	0.22

Table 3 includes the catalyst metals. This analysis involved actual gel-exposed finished device components (shell, patch, and gel). Tin levels are comparable to the FDA-approved saline-filled breast implants.

Table 3: Concentrations of Catalyst Metals Detected (in ppm by component weight).

Identification	Atomic Weight (amu)	PQL*	Implant Shell (ppm)	Patch (ppm)	Gel (ppm)
Tin	118.71	0.01	0.05	6.60	0.06
Platinum	195.08	0.01	3.30	2.60	4.00

*practical quantitation limit

3. PRECLINICAL – TOXICOLOGY DATA

Below is a review of the toxicology data.

Pharmacokinetics

Pharmacokinetics via Absorption and Disposition Studies describes an experiment in which the ^{14}C-labeled gel was implanted subcutaneously along the lumbar spine of 5 rats. The average dose was 3.4g of gel per 125g rat, equivalent to 27g/kg. One of the 5 rats was necrotic in the region of the implant, and another was severely debilitated, so the final results are based on only 3 rats. The ^{14}C-labeled silicone compound [redacted] was formulated to be identical to the standard polymer silicone used to manufacture implant gel. Following the subcutaneous implanting of the ^{14}C-labeled silicone gel, absorption, distribution, and excretion of the silicone gel was studied for up to 30 days post-implantation. After 30 days, virtually all of the labeled material was still at the implantation site. The amount of radioactivity collected from all other sites in the body accounted for only 0.06% of the administered dose. Levels of radioactivity peaked in the blood at day 21 and then declined. It is important to note that this gel was not encased in a shell, but was placed into the animal as a gel, yet only insignificant amounts were detected elsewhere in the organism at the end of 30 days.

Inamed provided a literature review on silicone pharmacokinetics. Inamed also cited a publication by Hine et al. 1969 (Toxicology and Applied Pharmacology, *15*, 566-573.). Given the experimental differences, the paper by Hine et al. is different but does not conflict with the Inamed results. Radio-labeled silicone oil was implanted in the peritoneal cavity. The molecular weight of the silicone oil in the gel is closer to 60,000 than to the 40,000 MW oil used by Hine. The oil in the gel is tightly bound to the gel. In Hine's experiment, 92% of the radioactivity was recovered from the peritoneal cavity 25 days after injection into that cavity. None was found in the urine, expired air, or feces. The testes had 1% of the radioactivity and the kidneys 0.6%. The migration that occurred may have been related to the lower molecular weight of the oil, the lack of binding to other components in the gel, and or to the larger surface area for absorption in the peritoneal cavity. The migration was not associated with toxic effects.

In the pharmacokinetic analysis, the distribution and elimination of silicones was measured by following the distribution of a ^{14}C-labeled polydimethylsiloxane oil incorporated into the gel formed from the same mixture used to make the production gel. This adequately reflects the rate of release of all silicone components. Though the label was in the oil, degradation of other components of the gel would result in the release of additional labeled oil, reflecting the degradation of the gel matrix to which the oil is bound.

In combination with the pharmacokinetic reports in the literature and the chemistry and toxicology evaluations provided specifically for this device, it is unlikely that additional pharmacokinetic analyses would provide information that would change our assessment of the safety or effectiveness of the device. FDA believes that the pharmacokinetic information is complete.

Cytotoxicity via USP Elution Test

Inamed submitted complete test results on MEM elution extracts of gel, Intrashiel shell, and leaf valve overlay assembly. No cytotoxicity was noted at 24 or 48 hours. FDA believes that this

testing is complete.

Sensitization via Guinea Pig Maximization Test

Inamed submitted complete test results on saline and sesame seed oil extracts of gel, Intrashiel shell, and leaf valve overlay assembly. No sensitization was detected. FDA believes that this testing is complete.

90-Day Intramuscular Implantation Test with Histopathology in Rabbits

Inamed submitted complete test results on direct implantation (90 days) of gel, Intrashiel shell, leaf valve overlay, and patch overlay. In no case was the reaction to any of the test articles more pronounced than that to the negative control article. FDA believes that this testing is complete.

Acute Systemic Toxicity and Irritation via the Class V Toxicity Test in Mice and Rabbits

Inamed submitted complete test results on the Class V Toxicity Test in Mice and Rabbits that determined the acute toxicity following intravenous or intraperitoneal injections in mice or intracutaneous injection in rabbits. Saline, alcohol, sesame seed oil, and PEG 400 extracts of gel, Intrashiel shell, and leaf valve overlay were used. None of the extracts of any of the test articles produced any signs of systemic toxicity or of intracutaneous reactivity in any of the mice or rabbits tested. FDA believes that this testing is complete.

Hemolysis via Direct Contact Acute Hemolysis Test

Inamed submitted complete test results on the Direct Contact Acute Hemolysis Test performed on gel, Intrashiel shell, and leaf valve overlay. Under the conditions of the test all of the test materials were negative for hemolytic activity. FDA believes that this testing is complete.

Pyrogenicity via the Acute Pyrogenicity Test in Rabbits

Inamed submitted complete test results on acute pyrogenicity of gel, Intrashiel shell, and leaf valve overlay. Under the conditions of the test all of the implant components were free of pyrogenic substances. FDA believes that this testing is complete.

Subchronic Toxicity

1. RTV Shell, Diaphragm Valve and Plug Assembly, Leaf Valve and Overlay Assembly, and Patch and Overlay Assembly

This is a 90-day subchronic subcutaneous implantation study in rats. The RTV shell is the shell used in the saline-filled implant manufactured by Inamed, but it also includes the same materials as the subject gel-filled device and is, therefore, applicable.

Each of four groups of 25 Fisher 344 female rats was implanted with 2 grams of sterile pulverized material from one of the four test articles. A fifth group of animals underwent the surgical procedure without implantation. Five deaths occurred within 24 hours of surgery; 2 in the sham control group, two in the leaf valve group, and one in the RTV shell group. These were all attributed to the stress related to surgery. The histological observations were consistent with presence of implanted foreign material.

After two weeks, the groups were reduced to 20 animals each. Animals were observed daily for toxicity. After 13 weeks, blood samples were taken for hematology and clinical chemistry

analyses. The animals were killed, organs were weighed, tissues were examined, and selected tissues were examined histologically.

Lesions at the surgical site were those expected to be seen secondary to surgery and the implantation of foreign material. These included lesions such as edema, eschar formation, and loss of surgical staples. Lesions observed at other sites were consistent with lesions commonly seen in Fischer 344 rats.

The mean percent lymphocytes were significantly lower and the percent neutrophils significantly higher in the implanted groups. The differences were small, and may be related to the inflammatory response to the foreign materials implanted. The only clinical chemical change was a lower mean albumin level in the leaf valve group. The value was small, and there were no correlative gross or histological changes associated with this observation.

There were no significant systemic effects. There were no medically significant differences at sites remote from the implant site. The local effects seen could all be attributed to a normal foreign response at the implant site.

2. [redacted] Gel and Intrashiel® Shell

Inamed provided subchronic testing of the [redacted] gel. The [redacted] is the silicone gel. The Intrashiel® shell is the phenyl/phenyl shell used in the gel implant. Empty gelatin capsules were used to implant the ground silicone materials. The purpose of the study was to determine the local tissue reaction to subcutaneously implanted components of the gel mammary implant and the low density polyethylene (LDP) reference control. The study compared the local reaction of the tissues to these materials which give rise to foreign body tumors at varying frequencies.

Edema and eschar were the only lesions seen at the implant site during the first 14 days after surgery. In general, the reactions at the implant site were mild. The gel never developed a grossly visible reaction at the implant site. There were also histological differences between the solid materials and the gel. The solid materials showed delicate connective tissue septa penetrating between the solid particles of the implanted materials. Penetration increased with time. By six weeks, the septa penetrated into all areas between the particles. The gel had a thin connective tissue layer surrounding, but not penetrating the mass. At three days there were neutrophils and lymphoid cells surrounding the mass, and, by 7 days, there was a trace chronic inflammatory reaction. This lasted throughout the study. Notably, there was a lack of granulomatous inflammation (multinucleated giant cells). The conclusion is that there were no significant differences between the solids, but the gel was associated with a less severe inflammatory response to the foreign material. The conclusion is that were no indications of excessive inflammatory responses associated with the gel or the elastomer components.

The phenyl/phenyl (P/P) elastomer and the polyethylene control both produced foreign body carcinogenesis in the chronic toxicity/carcinogenicity test, as expected. The elastomer treated animals had a shorter survival time and a shorter time to tumor formation. These differences in foreign body carcinogenesis may be related to the physical differences between the solid particles and the gel, as seen in this subchronic toxicity test.

As a whole, the subchronic toxicity testing is complete. The only remarkable response is the relative mild tissue response to the gel.

Reproductive and Teratogenicity Testing of Gel, Oils, and Elastomers

FDA's breast implant guidance recommends a 2-generation study. The compounds known to be associated with reproductive effects are the low molecular weight cyclic siloxanes, in particular, octamethylcyclotetrasiloxane, D_4 and D_5. These have been thought to act by reducing implantation of the fertilized egg and mean litter size. Below is a summary of the reproductive and teratogenicity testing.

1. Developmental Toxicity Study

The material tested was the [redacted] gel. Female Sprague-Dawley (CD) rats were used because there is a large database of previous studies and spontaneous transformations in this line. The females weighed from 150- 220 g at implantation. The doses were 0, 0.62, 7.3, and 14.8g/kg implanted between the scapulae. The animals were mated 1-week after implantation. At least 25 sperm positive females (i.e., evidence of mating) were assessed from each group. The animals were killed and examined 20 days after the finding of sperm in the vagina. The gestation period was 21 to 23 days.

The highest exposure should be 27g/kg for a 60kg woman receiving two 800ml implants. The highest dose tested (14.8g/kg) is in the ballpark, but provides no margin of safety. No adverse events were seen. Interestingly, liver weights tended to decrease with dose. The gel appeared to increase the conception rate from 80% in the control group to 94% in the high dose group. There were no significant effects on fetal morphology, skeletal malformations, or visceral malformations. No maternal or fetal toxicity was seen.

The rate of low molecular weight cyclic siloxane leakage is low, and the serum levels are more directly related to the rate of release than to the total amount present. Based on an estimate of the rate of diffusion of silicone through silicone published by Hoan-My Do Luu and Joe Hutter, 2001 (Environmental Health Perspectives 109:1095-1101.), all of the D_4 would require at least 30 days to diffuse out of the prosthesis. The actual time is likely to be even slower, but this reduces the release by at least a factor of 30, providing a wider margin of safety.

2. Saline Implant Teratology Study

This study provided general information on silicones and includes data on patch material used in both saline and gel implants.

The study involved testing at a high dose of 21g/kg of ground shell. This dose is adequate, because it reflects the weight of the shell only, i.e., two 800ml saline implants contain only the weight of 2 shells, or about 40g (weight of the shell is 20 grams). If two shells correspond to a dose of 40g, the dose is 0.7g/kg (40 ÷ 60). The dose testing allows for a reasonable margin of safety.

The test animals had significantly more visceral abnormalities in the litters ($p<0.05$), but the control animals showed significantly more skeletal abnormalities. Although the differences were significant, they had little or no medical significance, and were reflected only in totals, not in any of the individual anatomical abnormalities. The data from this study and the study described above addresses the reproductive/teratogenicity testing for the patch, disk, and RTV adhesive and the gel.

3. Female Fertility and Developmental Toxicity Study

Reproductive toxicology on the phenyl/phenyl shell was requested because compounds such as cis-2,6-diphenylhexamethylcyclotetrasiloxane are known to have estrogenic activity (IOM Report, p.103).

The developmental study in rats had two groups of 35 males and 40 females each. The control females were sham operated. The test females were implanted with 2g of pulverized Intrashiel® shell. After 5 weeks of recovery, 35 females were randomly selected from each group and mated "until at least 28 females in each group exhibited positive evidence of mating." Thirty-five sham operated females and 34-implanted females were mated. One female died prior to mating from an overdose of anesthetic while the staples were being removed. One male died with acute edema and congestion in the lungs and meninges, and was not replaced. No other animals died or were euthanized.

On day 21 of gestation, presumed pregnant females were killed; each ovarian horn was identified and removed with the corresponding ovary. The numbers of corpora lutea on each ovary were counted. The locations, numbers, and sex of each and life or death status was recorded for each fetus. The fetuses were examined for external anomalies, and placed in Bouin's or 70% alcohol.

One animal delivered on day 21, prior to C-section. The pups were examined for gross appearance but were excluded from the C-section observations. There is no report as to whether they were live or dead. The animals weighted about 150g at the time of surgery and 161g at the time of mating.

Female Developmental and Fetal Evaluations - There were no significant differences in the C-section observations. Fetal observations were based on 418 sham and 448 fetuses from treated animals, corresponding with 27 sham and 28 implanted animals. The numbers of fetuses with any alteration were equivalent in the control and treated groups. The mean number of fetuses with any alteration was 0.9 in the sham group and 1.0 in the test group, with standard deviations of 2.3. One fetus (135-11, an implanted animal) had multiple anomalies, and showed up in several tables. There were no significant differences in the frequencies of gross external, soft tissue, or skeletal changes in the treated as compared to the sham control group.

Fertility Effects - Fertility was 89% in the sham group and 82% in the treatment group. The difference is not significant. There were 30 animals in the control group and 28 in the implanted group.

In summary:

1. The implanted shell had no effect on litter size or the fetal incidence of gross external, soft tissue or skeletal alterations. The fertility index (no. of pregnancies x 100/no. of matings) was 89% in the sham control and 82% in the test group. This difference is not significant.

2. There were actually 30 control and 28 test litters with live fetuses. Three control animals were excluded because the litter sizes were considered atypical (i.e., they had less than 5 live fetuses, reducing the sample sizes to 27 control and 28 treatment rats). Caesarean-sectioning data are based on 27 and 28 pregnant rats with 5 or more live fetuses. The fact

that the small litters were in the control rat populations limits the concern about the effects of silicone materials on fecundity.

3. The largest shell, for the 800ml implant, weighs 52g. If there were 2 of these in a 60kg woman, the exposure would be 104g/60 kg, or 1.7g/kg. The rats received 2 g and the average weight at implantation was 150 g, so the dose was 13.3g/kg. This is not quite a factor of 10, but it is a high reasonably close dose.

This report satisfies the teratogenicity testing for the Intrashiel® shell and provides a well executed 1-generation reproductive toxicology report.

4. Extended 1-Generation/2-Generation Reproductive Study with Histology

Inamed proposed an extended 1-generation study rather than a 2-generation study. In this study, the F1 animals are followed to puberty to detect, for example, a DES problem, in which the F1 generation develops lesions at the time of puberty. The study would also contain histology of the uterus and ovaries of the F1 animals at puberty. Thus, FDA was expecting an extended 1-generation study.

Inamed addressed the extended 1-generation study by selecting animals from an in-progress 2-generation study. The Fo animals were bred to produce the F1 generation, and 4 weeks after implantation of the Intrashiel® shell, the F1 animals were bred to produce an F2 generation. Thus, data were obtained from 2 generations of progeny. Given that data were provided from 2 generations, the extended 1-generation study added additional histological support to the other studies.

Test article was prepared by pulverizing the Intrashiel shell in liquid nitrogen to achieve a particle size ranging from 1 to 0.3mm. The dose administered per rat was 2g.

Mating was begun 4 or 5 weeks after surgery and was repeated until at least 28 females in each group showed positive evidence of mating (vaginal semen or semen plug). The fertility index was recorded as the number of live litters divided by the number of positive matings.

Following the lactation period, sufficient F1 pups were selected to produce the F2 generation. At 5 or 6 weeks, the animals underwent sham or implantation surgery as described for the Fo animals. Four or 5 weeks later, the animals were mated until at least 24 females showed positive evidence of mating.

Some animals were killed to get the tissues for the histological information requested by FDA. Tissues were preserved in formalin and processed into H & E stains, as required. Both males and females were examined histologically. Female tissues included uterine horns, cervix, fallopian tubes, adrenal glands, pituitary, and ovaries.

Surgical Site Observations - At the surgical sites, the Fo and F1 animals had similar wound-related pathology.

Clinical Observations - There were no clinical signs of toxicity in the control or implanted groups in either the Fo or the F1 generation.

Reproductive Performance - All groups were considered normal.

Test Group	# Mated	Mating Index	Fertility Index	Mean Gestation Time (days)
F0				
Sham Control	35	80%	96%	21.9
Implanted	35	74%	96%	21.6
F1				
Sham Control	30	80%	92%	21.6
Implanted	30	90%	96%	21.6

The number of pups born and surviving was not significantly different in any of the test groups.

Gross Findings - There were no significant differences in gross findings between the sham and implanted groups in either the Fo or F1 groups, nor were there difference between the Fo and F1 groups.

Histological Findings - There were no histological differences between the F1 male sham and patched groups. Each had 2 categories of lesions:

1. Lymphocytic infiltrates in the stroma of the epididymides and/or prostate gland
2. Foci of glandular dysplasia in the prostate gland.

In the F1 female group there were 2-treatment related lesions:

1. a single case of a cystic granulomatous lesion at the site of implantation
2. "a single granulomatous paroophoritis associated with implant material."

One implanted female had inflammatory lesions of the parovarian tissues and another had embryonic rests of tissues in the pituitary gland. The data indicate that these unique findings occurred in single animals only, which reduces the concern.

The granulomatous lesion at the implant site is in contact with the implant and is consistent with a reaction to a foreign body. FDA requested Inamed to address the paroophoron lesion, and in particular, whether it is device related. The internal lesion, away from the implant site seemed enigmatic. Inamed explained that the body wall was accidentally breached during the implantation process, and the implant material got into the retroperitoneal space. Therefore, it was an expected foreign body reaction.

The other unusual finding was a report of some deaths in the F1 sham-control animals due to the placement of identification programmed transponders. These deaths seemed strange, because the same transponders were presumably used in the Fo animals. FDA requested Inamed to address this. Inamed stated that the deaths were accidental deaths due to an overdose of isoflurane used as the anesthetic for the placement of the transponders. This did not affect the testing.

Inamed concluded that the reproductive competency in both the Fo and F1 generations and the normalcy of the F2-litters indicates a lack of significant reproductive and teratogenic toxicity.

FDA believes that this reproductive/teratogenicity testing is complete.

Immunotoxicology Data

1. Patch and Overlay Assembly

Female B6CF1 mice were implanted with 56.5 mm^2, 113 mm^2, or 226 mm^2 pieces of the patch and overlay assembly. Twenty nine days later, the animals were killed and examined for effects on the immune system.

There were no significant changes in erythrocyte number, hemoglobin, hematocrit, red cell indices, platelets, or leukocyte numbers, or differentials. There were no changes in spleen or thymus weights or changes in gross pathology.

There were several effects on other parts of the immune system. Spleen cell numbers were reduced in the middle and high dose groups. B cells were reduced about 15%, total T cells by 29%, T helper cells by 25%, and T suppressor cells by 14%. Natural killer (NK) cells were reduced by 33% compared to the sham control. Antibody forming cells in the spleen showed a trend of reduction, but the changes were not significant. The normality of the antibody forming cells is important, because it indicates that a complex immune function was not significantly affected, even though cell counts were reduced. All changes were significantly less than the effects of the positive control, cyclophosphamide (25mg/kg).

2. Leaf Valve and Overlay Assembly

The protocol for this experiment was the same as the protocol described above, but the leaf valve and overlay assemblies were implanted. The same areas of these components were used.

There were no significant changes to the immune system. There were low eosinophils at the low dose and a 28% increase in the IgM antibody forming cells in the spleen at the middle dose measured as specific activity (cells/10^6 spleen cells), but this was not significant in the total spleen and was not dose dependent. NK cells were reduced 25% (measured as NK activity) and by 31% in total spleen activity at the middle dose, but not at the low or high doses.

The mixed lymphocyte response was somewhat troubling, because it showed a clear dose effect with the response decreasing with dose. None of the individual levels reached significance, but the highest dose produced a response about midway between the sham control and the cyclophosphamide positive control. It appears as though the differences between the positive control and the cell numbers and the radioactivity for the highest dose were significantly different from the sham control. The testing of the Diaphragm valve and plug assembly produced a decrease (but not statistically significant) in the mixed lymphocyte response with dose (see Test #3 below).

There was no evidence of biologically significant immunotoxicity.

3. Diaphragm Valve and Plug Assembly

This employed the same battery of tests used in the above immunotoxicity testing. There were two immunological changes observed. There was a significant increase in the spleen weight at the medium dose level. This was not dose related, and the histological examination reported that the spleen was normal. This is not likely to be an issue. The second change was a decrease in the NK cell activity. There were statistically significant decreases in both the low (40%) and the medium doses (35%), respectively, but the high dose was not significantly different from the

control. These were comprehensive studies, and with this change unrelated to dose, it is difficult to consider these effects biologically significant.

4. BIOCELL® INTRASHIEL® Shell

This employed the same battery of tests used in the above immunotoxicity testing. The outliers in this test were an increase in the number of antibody forming cells (AFC) and a decrease in the $CD4^+CD8^+$ cell population. The AFC cell increase showed a dose-response relationship, but was significant at the highest doses only. This was attributed to "a historically low sham control."

FDA believes some results are ambiguous, but, unless they are consistent with other indicators of immune function, they are not likely to be biologically significant. For example, the 37% decrease in the $CD4^+CD8^+$ population relates to the cells that "make up a very small percentage of the spleen population, usually less than 4%, and thus, very slight changes in cell number can result in statistical differences without functional relevance." Some of this small population is, however, an important population, because it is the precursor population for the $CD4^+$ and the $CD8^+$ cells. Nevertheless, no effects were seen on the complex immune function of IgM plaque formation, so the $CD4^+CD8^+$ decrease may not have been biologically significant. The variation associated with the testing must also be considered. The concordance of the plaque forming cell assay with known positive and negative materials was only 78%, which highlights the variability of the testing.

FDA agrees with Inamed that the implantation of the INTRASHIEL® shell did not adversely affect the functional ability of the immune system. The immunotoxicology tests all showed wide variations. These results appear to fall within the variation for these experimental techniques.

5. Silicone Gel

This employed the same battery of tests used in the above immunotoxicity testing. Again, most results were normal. The anomalies in this testing were an increase in the mean corpuscular volume and a 16% increase in spleen weight, both observed at the highest dose only. In the absence of dose-related responses and the involvement of unrelated parameters, FDA believes that this testing is adequate.

Inamed also submitted a follow-up to the above study to provide a histological assessment of the 16% splenic weight increase. Because the spleens were used as a source of cells in the above experiment, the spleens were not available for histology. B6C3F1 mice were injected with 2 or 3 ml of the gel. On day 29, the mice were killed. The variables assessed were body weight gains, general observations, and terminal spleen weights and histology. The spleens were not increased in weight in this experiment and the histology was normal. In the middle dose group, the spleen weight was significantly decreased. Spleen histopathology was not affected.

The amounts of test articles were presented as the areas of the material tested. Inamed then converted these to weights for calculating exposures. It is clear that the highest animal doses were higher than the highest anticipated human exposure. In addition to the dose comparisons, it should be pointed out that the positive results seem to be random, in that there are no patterns consistent with immune stimulation or inhibition. For example, in the testing of the Intrashiel shell, there was a dose-related increase in splenic antibody forming cells, though only the cell increase at the highest concentration was significant. In the same experiment, the sham control

was lower-than-normal. There was no evidence of a biologically significant immune effect in this test.

As a whole, FDA belies that the immunotoxicology testing is complete.

Genotoxicity

1. Bacterial Mutagenicity via Reverse Mutation Assay in *Salmonella typhimurium* (Ames Test)

Inamed submitted complete test results on bacterial mutagenesis studies with DMSO extracts and with a combined ethanol extract of gel, Intrashiel shell, [redacted], leaf valve overlay, and RTV shell. None of the extracts, with or without microsomal fraction activation, were mutagenic to any of the bacterial tester strains. FDA believes that bacterial mutagenesis has been adequately addressed.

2. Mammalian Mutagenicity Testing via CHO/HGPRT Forward Mutation Assay

Inamed submitted complete test results on the CHO/HGPRT Forward Mutation Assay with a combined ethanol extract of gel, Intrashiel shell, UHP shell, leaf valve overlay, and RTV shell. None of the extracts, with or without microsomal activation, were mutagenic or cytotoxic to the CHO cell cultures. FDA believes that mammalian mutagenesis has been adequately addressed.

3. DNA Damage via Chromosomal Aberration Frequencies in CHO Cells

Inamed submitted complete test results on an *in vitro* cytogenetic assay which measured chromosomal aberration frequencies in CHO cells with a combined ethanol extract of gel, Intrashiel shell, UHP shell, leaf valve overlay, and RTV shell. No significant increase in cells with chromosomal aberrations was seen at any dose level in either the absence or presence of rat liver microsomes. FDA believes that DNA damage has been adequately addressed by this assay.

Cell Transformation

Inamed provided testing with a transformation assay on the saline-filled device. This is satisfactory for the valve and patch assemblies, but we are primarily interested in the gel-specific materials (i.e., the Inamed gel and the phenyl/phenyl low-permeability shell).

Inamed also provided a transformation assay report in BALB/C-3T3 cells using a silicone gel that is similar to the material used in this product. These were performed in culture medium and ethanol extracts. These tests showed no transformation. This supports safety by demonstrating that a closely related material does not cause transformations in mammalian cells.

Inamed provided Salmonella genotoxicity tests on DMSO extracts of the phenyl/phenyl shell, the [redacted] gel, and the leaf valve assembly. The extracts did not increase the number of revertants in the presence or absence of S9 activation.

Inamed provided a test involving a combined ethanol extract of five mammary implant components in the Salmonella mutagenesis test system. The 5 items tested were the [redacted] gel, the leaf valve assembly, the phenyl/phenyl shell, UHP shell, and the RTV shell. The shell materials were extracted at 120cm^2 per 20ml of absolute ethanol. The gel and valve assembly were extracted at 4g per 20ml. The extractions were conducted at 70°C for 24 hours. Equal volumes of each extract were combined, and concentrated by evaporation at 5°C under a stream

of nitrogen. Extracts were tested at 5, 10, 25, 50, and 100µl per plate. None of the extracts increased the reversion rate beyond the control level.

Inamed provided a 5-material ethanol extract test evaluating chromosomal aberrations tests in Chinese Hamster Ovary (CHO) Cells. The five materials extracted were [redacted], leaf valve assembly, phenyl/phenyl shell, UHP shell, and RTV shell. The RTV shell included extracts from McGhan Nusil, Polymer Tech, and Applied Silicone. Each of the materials was extracted individually. Ten or 15ml of the extracts were combined and evaporated down at 70°C so that the final volume was 10 or 15ml. The tests were conducted with and without microsomal (S9) activation. The combined extract was considered negative for inducing chromosomal aberrations.

Inamed provided a combined alcohol extracts test for CHO/HGPRT forward mutation testing. The extracts were prepared as described previously. Testing was performed with and without microsomal activation. The extracts did not increase the forward mutation rate.

Chronic Toxicity/Carcinogenicity Testing

1. Chronic Toxicity/Carcinogenesis Testing of the Phenyl/Phenyl Elastomer

This was a 2-year carcinogenicity testing involving 3 groups of Fisher 344 rats. The animals followed in the study were: 119 sham control animals; 111 LDP reference control animals; and 110 implanted with phenyl/phenyl shell. The Group 1 animals were sham operated, and had no implants. Group 2, the control group, was implanted with Low Density Polyethylene (LDP). The polyethylene was pulverized, packed in 000 gelatin capsules and implanted. The Group 3 animals got the phenyl/phenyl elastomer pulverized and implanted in 000 gelatin capsules in the same way as the polyethylene control. The animals were followed for 2 years.

The carcinogenicity testing of the phenyl/phenyl (P/P) shell showed that the polyethylene control and the P/P elastomer (pulverized and delivered in gelatin capsules) both caused foreign-body carcinogenesis. However, compared to the low density polyethylene (LDP), the P/P-exposed animals had significantly shorter survival times, and shorter times to tumor formation (tumor latency). This is likely because of physical differences in the materials. Published reports have ascribed such findings to differences in surface characteristics.

Probabilities of Paired Observations

Observation	Paired Groups	P
Overall survival	P/P[1] or LDP[2] versus sham control	<0.01
	P/P versus LDP	<0.01
Time to tumor	P/P versus sham control	<0.05
	LDP versus sham control	NS
Time to death	P/P versus LDP	NS
	P/P versus sham control	<0.05

[1]Phenyl/phenyl shell
[2]Low density polyethylene

The overall survival differences were based on the 119 sham, 111 LDP, and 110 phenyl/phenyl animals. When performing the statistical analysis, all animals that died during the study were included (scheduled sacrifice and terminal sacrificed animals were censored). There was no significant difference in survival time when animals with implant-site tumors were removed.

The biologically important difference is the difference between the LDP control and the P/P. The differences between the sham control and the materials are accepted as foreign body carcinogenesis. The differences between the materials, though statistically significant, are small. It is helpful to note some of the actual numbers of animals. For example, the 13- to 18-month mortalities for the sham, LDP, and P/P groups were 6/106, 15/101, and 20/92. The difference between the materials is much less impressive than the differences between the materials and the sham control. Differences in the relationships between surface texture and tumor responses were also seen in the study of the gel.

2. Carcinogenicity of the Gel ([redacted])

This experiment tested for carcinogenicity of the gel in the gel implant. It was performed the same way as the experiment described above. The results were the opposite (i.e., the test device had a longer time-to-tumor and a longer survival time than the polyethylene control). There were about twice as many tumors in the control animals as in the gel-implanted animals. The gel produced fewer tumors (34) than any of the other materials tested. The mean number of tumors from 4 elastomer studies was 70 ± 5 tumors. The patch and overlay assembly and the diaphragm valve and plugs assembly each produced 26 and 21 tumors, which were the lowest numbers produced.

As discussed above, papers have been published on the relationships between the texture of the material and tumor formation. Polyethylene disks with smooth surface produced more tumors than the same material with a rough surface (Bates, R.R. and Klein, 1966. M. J. Natl. Cancer Inst. *37*: 145). Inamed used this to explain the differences between the various materials tested.

3. Carcinogenicity of Diaphragm Valve and Plug Assembly, Leaf Valve and Overlay, Assembly and Patch and Overlay Assembly

The experiment was conducted with 4 groups of Fischer 344 rats. Each group had 120 animals plus a satellite group of 20 animals and 10 replacement animals.

- Group 1 Sham Control
- Group 2 Valve/Plug
- Group 3 Valve Overlay
- Group 4 Patch Overlay.

Except for the sham controls group, the animals were all implanted with 2g of pulverized device. The powder was introduced directly into a large surgically prepared subcutaneous pocket throughout the entire dorsal region, down the shoulders, down the flanks, and over the outer surface of the thighs. This dispersal over a wide area appears to have limited, but did not eliminate the foreign body response.

The time to tumor was significantly different from the sham control in all 3 test groups. The time to death was not different from the sham control in any group. There was no indication of systemic toxicity or carcinogenicity, except for the foreign-body tumors seen. The foreign-body reaction is not believed to occur in humans or occurs at very low frequency.

As a whole, FDA believes that the carcinogenicity testing is complete. The testing provided no evidence of carcinogenic materials in the gel-filled prosthesis.

4. PRECLINICAL – MECHANICAL DATA

Below is a review of the mechanical data.

Fatigue Rupture Testing of Total Device

Fatigue rupture testing assesses the number of cycles at specific applied loads that a device can endure until it ruptures. Standard production Style 40 and Style 110 implants, representative of Inamed's gel-filled devices, were tested. The testing was performed based on worst case device testing (i.e., smallest size and thinnest shell). The following was determined to be worst case:

Style	Surface	Size (cc)	Thickness (in)
40	Smooth	80	0.013
110	BIOCELL® Textured	90	0.018

The testing was conducted with applied load control equipment and involved compression of the implants between 2 metal flat plates. Testing was performed at 1 Hz, which is the frequency of loading during walking and avoids undesirable heating at higher frequencies. Three (3) implants of each Style (40 and 110) were tested at each applied load level (20, 30, 40, and 55 lbs) until failure or 6.5 million cycles runout (RO) was reached. RO was defined as 6.5M cycles, which was based on 1 step per second for 5 hours per day for 1 year. In addition, the fatigue testing included determining the ultimate static load (i.e., force to failure due to a single compression of an implant).

The results were:

	Style 40 (smooth)	Style 110 (textured)
Ultimate Static Load	1245 lbs[1]	1861 lbs[1]
Endurance Load Limit at 6.5M cycles runout	55 lbs[2]	+30 lbs[3]

[1]Static failure loads are greater than that expected during mammography (55 lbs).
[2]All samples made it to RO without failure. Because of time restraints, no further testing was performed to see if the endurance load limit was greater than 55 lbs for Style 40.
[3]1 of 3 samples failed at 6.1M cycles at 40 lbs while the other 2 made it to RO. Therefore, the endurance load limit for Style 110 is probably closer to 40 lbs. However, for worst case purposes, it is noted at 30 lbs, the load at which all samples made it to RO.

Applied load averages were calculated for all applied load test cycles and AF/N curves were generated. The endurance load limit, below which an implant can undergo an unlimited number of cycles without failure, was determined to be 55 lbs for Style 40 implants and 30 lbs for Style 110 devices (as shown in the table above).

The acceptance criteria for the fatigue testing were:

- 100% runout to 6.5M cycles at *in-vivo* load (i.e., 3.7 lbs rounded to 5 lbs);
- 100% runout at twice the *in-vivo* load (i.e., 10 lbs); and
- evidence that the *in-vivo* load is past the inflection point of the AF/N curve.

As noted above, the acceptance criteria already have a built-in safety factor (SF) of >2 and the fatigue results met these criteria. As compared to the expected in-vivo load of 3.7 lbs, the fatigue results had a SF of 14.8 for Style 40 and a SF of 8.1 for Style 110.

Cohesivity Testing of Silicone Gel

Gel cohesivity and penetration testing assess the cohesive and cure characteristics of silicone gel, respectively.

Gel cohesion testing was performed as per ASTM F703 (cone/pendant method). The gel was taken from final production implants. Of the 112 samples tested, the average pendant length was 0.34cm (range of 0.0-1.1cm), which is below the ASTM F703 specification of <4.5cm.

Gel penetration was an in-process test performed at gel assembly time. Although there is no standard for gel penetrometer testing, the general test methodology involves measuring the distance a probe traveled into the gel held in a test holder. Of the 112 samples tested, the average penetrometer reading was 49.2 penetrometer units (range of 39.5-56.0 gel penetrometer units). The Inamed specification for cured gel is [redacted] penetrometer units. Thus, the results met Inamed's specifications.

Bleed Rate Testing of Silicone Gel

Gel bleed testing assesses the diffusion rates of silicone gel through the shell. Gel bleed testing was performed as per ASTM F703. Testing was completed on Style 40 (smooth; 80cc, 0.013" thickness) and Style 110 (textured; 90cc, 0.018" thickness), which were considered representative of Inamed's silicone gel product line. All implants were fabricated in standard production and sterilized prior to testing. The tested implants were the smallest size with the minimum thickness at least at 1 point on the shell radius. As per ASTM F703, gravimetric weight gain measurements were taken at weekly intervals for a period of 8 weeks.

Inamed also provided previous gel bleed testing performed on their device; however, the shell thickness values for that testing were not measured. The results from this new testing, along with the previous data, are summarized in the table below.

Style	N	Normalized Weight Gain at 8 Weeks (g/cm^2)	Normalized Weight Gain Rate at 8 Weeks (g/cm^2/week)	Shell Thickness (in)
40 (new data)	10	0.0152	0.0019	0.0125-0.020
40 (old data)	12	0.0130	0.0016	None taken
110 (new data)	10	0.0048	0.0006	0.0175-0.0260
110 (old data)	12	0.004	0.0005	None taken

There are no accepted performance standards for gel bleed testing. Inamed performed gel bleed testing as per the industry standard – ASTM F703. However, the ASTM F703 test method was not established to replicate physiological conditions but, instead, to accelerate the bleed diffusion process to compare various smooth implant designs. Another weakness of the ASTM F703 test method is that the control silicone disks, which are used to adjust for humidity, are fully exposed as compared to the test silicone disks that are covered by the implants. Thus, the adequacy of the gel bleed results cannot be determined.

5. PRECLINICAL - RETRIEVAL STUDY

The purpose of the retrieval study was to better understand possible modes of gel-filled breast implant failure *in vivo*, which could lead to improvements in manufacturing, device design, surgical techniques, and/or labeling.

Inamed's retrieval study focused on explanted gel-filled implants associated with a complaint, which includes both ruptured and non-ruptured devices. Inamed defines a "complaint" as "any written, electronic or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a device after it is released from distribution." Typically, when a physician has an explant to return, his or her office calls Inamed's Product Support group, who in turn send the physician the appropriate paperwork to fill out and return with the explant.

There was no requirement that an explanted device be returned to Inamed for inclusion in their retrieval study; however, Inamed was expected to make a good-faith effort to obtain any explanted device Styles 10, 20, 40, 45, 110, 120, and 153 for inclusion into the retrieval study. There were 339 silicone gel devices retrieved between 7/31/00 and 10/1/02. This includes 10 devices from the Core Study and 141 devices from the Adjunct Study, which comprises 45% of the 339 implants in the retrieval study. The 188 devices were either implanted prior to the call for PMAs, were returned unused due to an intraoperative observation, or are unknown (e.g., no serial number could be identified to link to a study).

Physician and Laboratory Observations

The table below summarizes the device observations made by the physicians at the time of explantation. 133 (39%) of the 339 retrieved implants were noted to be ruptured by the physician and 114 were noted as non-ruptured.

Physician Observation	Style 10	Style 20	Style 40	Style 45	Style 110	Style 120	Style 153	Total
Total retrieved from 7/31/00 and 10/1/02	1	0	75	41	67	29	126	339
Ruptured[1]	0	0	21	10	28	11	63	133
Non-ruptured[2]	0	0	31	19	19	10	35	114
Intra-operative[3]	0	0	11	6	7	1	21	46
No information[4]	1	0	12	6	13	7	7	46

[1]Reported by physician to have opening(s) in shell.
[2]Reported by physician to not have any opening(s) in shell.
[3]Reported by physician as unsuitable for implantation during the surgery (e.g.; accidental puncture of implant intraoperatively; physician had an issue with the packaging, size or style of the device; physician noticed a particle or fiber on the device or in the packaging)
[4]Reported as explanted devices by physician, but Inamed had not received the necessary paperwork on the implant.

After receipt of the explanted device, Inamed's laboratory assessed the device characteristics independent of the physician's observation. The device characteristics observed in the laboratory were stratified into 6 categories:

- Smooth-edge openings were devices reported by the laboratory to have an opening associated with fold-flaw.

- Sharp-edge openings were devices reported by the laboratory to have an opening not associated with fold-flaw.
- "Broken devices" were reported by the laboratory to be received in a state where minimal analysis can be performed. Examples included shell torn in separate pieces or a device with gel only and a few or no pieces of shell sticking to it.
- Device surface observations were devices reported by the laboratory as having no openings but observations were made. Examples included a scalloping around the radius, dimpling of the implant, and "shaped" device returned by the physician that was "round" device.
- Gel-related observations were devices reported by the laboratory as having no openings but observations were made. Examples included particles or bubbles in the gel.
- "Functional" devices were devices reported by the laboratory as having no openings and no failure characteristic could be identified.

Although a device could have one or more of the characteristics above, Inamed provided only the primary device characteristic using a hierarchy defined by the order of the bullets above. In other words, if a device was found to have both smooth-edge and sharp-edge openings, it was reported as a smooth-edge opening.

The table below summarizes the **primary device characteristics observed by the laboratory for the ruptured devices ("ruptured" as per the physician observation).** 22 (17%) of the 133 noted ruptured by the physician were found to be functional by the laboratory. If you consider device surface observations and gel-related observations, because neither of these include openings, then 33 (25%) of those noted ruptured by the physician were found to not have openings by the laboratory. Only 2 (2%) of the ruptured implants had smooth-edge openings. Overall, assuming broken devices are confirmed ruptures, then 100 (75%) of the ruptured devices were confirmed as ruptured by the laboratory.

Primary Laboratory Observations of "Ruptured" Devices[1]	Style 10	Style 20	Style 40	Style 45	Style 110	Style 120	Style 153	Total
Ruptured	0	0	21	10	28	11	63	133
Smooth-edge openings (at crease)	0	0	2 (10%)	0	0	0	0	2 (2%)
Sharp-edge openings (not at crease)	0	0	7 (33%)	5 (50%)	15 (54%)	6 (55%)	47 (75%)	80 (60%)
"Broken device"	0	0	7 (33%)	3 (30%)	6 (21%)	1 (9%)	1 (2%)	18 (14%)
Device surface observations	0	0	0	0	0	0	4 (6%)	4 (3%)
Gel-related observations	0	0	0	0	2 (7%)	0	5 (8%)	7 (5%)
"Functional"	0	0	5 (24%)	2 (20%)	5 (18%)	4 (36%)	6 (10%)	22 (17%)

[1]The denominators used to determine the percentages were based on the number of ruptures for the given style. The hierarchy for determining the primary device characteristic was smooth-edge opening, sharp-edge opening, "broken device," device surface observations, gel-related observations, and "functional."

The table below summarizes the **primary device characteristics for non-ruptured devices ("non-ruptured" as per the physician observation).** 11 (10%) of the 114 noted non-ruptured by the physician were found to have sharp-edge openings by the laboratory. If you consider broken devices, then 13 (12%) of those noted non-ruptured by the physician were found to have openings by the laboratory. 88 (77%) of the 114 devices were found to be functional by the laboratory (i.e., they were not ruptured). 11 (10%) of the 114 devices had sharp-edge openings, which may be due to the fact that the physician missed that the device was ruptured and/or the physician cut the device upon implantation or explantation. Overall, assuming broken devices are confirmed ruptures, then 101 (89%) of the 114 non-ruptured devices were confirmed as non-ruptured by the laboratory. Accordingly, 11% of those devices reported as non-ruptured were ruptured.

Primary Laboratory Observations of "Non-Ruptured" Devices[1]	Style 10	Style 20	Style 40	Style 45	Style 110	Style 120	Style 153	Total
Non-ruptured	0	0	31	19	19	10	35	114
Smooth-edge openings (at crease)	0	0	0	0	0	0	0	0
Sharp-edge openings (not at crease)	0	0	3 (10%)	1 (5%)	1 (5%)	1 (10%)	5 (14%)	11 (10%)
"Broken device"	0	0	1 (3%)	0	1 (5%)	0	0	2 (2%)
Device surface observations	0	0	0	1 (5%)	0	0	2 (6%)	3 (3%)
Gel-related observations	0	0	3 (10%)	2 (11%)	1 (5%)	0	4 (11%)	10 (9%)
"Functional"	0	0	24 (77%)	15 (79%)	16 (84%)	9 (90%)	24 (69%)	88 (77%)

[1]The denominators used to determine the percentages were based on the number of non-ruptures for the given style. The hierarchy for determining the primary device characteristic is: smooth-edge opening; sharp-edge opening; "broken device"; device surface observations; gel-related observations; and "functional."

The following is an overall discussion of the results based on the laboratory observations:

- Smooth-edge openings rarely occurred or were associated with reports of rupture (2/339 or 0.6%).
- The predominate device failure characteristic for devices reported as ruptured was sharp-edge openings (80/133 or 60%).
- Of the 91 devices with sharp-edge openings, 82% were textured devices (Styles 110, 120, and 153) and 18% were smooth devices (Styles 10, 20, 40, and 45).
- ≈17% of devices reported as ruptured were observed in the laboratory to be "functional."
- ≈77% of all devices reported as non-ruptured were observed to be "functional."
- Of all devices reported as ruptured by the physicians, 75% were confirmed ruptured by the laboratory. The remainder of the devices was found to have no openings.
- Of all devices reported as non-ruptured by the physicians, 89% were confirmed as non-ruptured by the laboratory. The remainder of the devices was found to have openings.

The table below shows the device characteristic data on the intraoperative devices and explanted devices for which no other information is available; these data were pooled across styles.

However, based on the numbers involved, Inamed did not provide a discussion of those laboratory results.

Primary Laboratory Observations of "Intra-Operative" and "No Information" Devices	Intraoperative Devices (N=46)	Explanted, no Other Information (N=46)
Smooth-edge Openings (at crease)	0	0
Sharp-edge Openings (not at crease)	10	8
Broken device	0	1
Device Surface Observations	1	1
Gel-related Observations	17	6
Functional	18	30

Sharp-edge Analyses

Inamed referenced a separate technical study performed to characterize sharp-edge openings created by surgical instruments (TR-402) for their saline breast implant retrieval study. That study showed that Inamed could successfully replicate the sharp-edge openings with surgical instruments on sample devices. Therefore, unreported surgical damage to devices received can be identified and the opening is reported as "unreported surgical damage sharp-edge opening."

Accordingly, Inamed performed analyses on all devices in this retrieval study with sharp-edge openings, including the frequency at different locations on the shell and across styles. Inamed stated a sharp-edge opening was recorded as surgical damage only when reported by the physician, but not all sharp-edge openings created by surgical instruments may be reported by the physician.

Inamed's analyses showed that 16 implants had surgical damage reported by the physician and that Inamed observed unreported surgical damage on another 4, for a total of 20 devices observed to be surgically damaged. In summary, there were a total of 109 devices observed by the laboratory with sharp-edge openings: 80 ruptured, 11 non-ruptured, 10 "intraoperative," and 8 "explanted, no other information." Of those 109 devices with sharp-edge openings, 18% (20/109) had surgical damage.

Mechanical Testing

Inamed performed mechanical testing on the following devices for which the mode of failure could not be determined:

- Ruptured devices with sharp-edge characteristics observed by the laboratory
- Non-ruptured devices with sharp-edge characteristics observed by the laboratory
- Ruptured devices with no openings observed by the laboratory
- Non-ruptured devices with no openings observed by the laboratory.

However, destructive testing was not performed on a device, if requested by physician or hospital. The results of the mechanical testing were as follows:

Mechanical Test	Physician/Laboratory Observations	Smooth Implants (Styles 10, 20, 40, & 45)		Textured Implants (Styles 110, 120, & 153)	
		n	Ave.	n	Ave

Ultimate break force	Ruptured sharp-edge	3	6.8 lbs	17	4.0 lbs
	Non-ruptured sharp-edge	0	N/A	3	4.6 lbs
	Ruptured no openings	17	5.1 lbs	23	4.9 lbs
	Non-ruptured no openings	46	5.8 lbs	18	4.8 lbs
Ultimate elongation	Ruptured sharp-edge	3	613%	17	429%
	Non-ruptured sharp-edge	0	N/A	3	427%
	Ruptured no openings	17	565%	23	466%
	Non-ruptured no openings	24	613%	17	485%
Patch joint	Ruptured	2	5.7 lbs	7	5.8 lbs
	Non-ruptured	1	5.6 lbs	5	6.2 lbs
Bladder joint (Style 153 only)	Ruptured	N/A	N/A	5	5.8 lbs
	Non-ruptured	N/A	N/A	4	5.4 lbs

There was no statistical difference in physical properties between devices reported as ruptured or non-ruptured. Therefore, the mechanical testing did not help assess the modes of failure.

Modes of Failure

For each device characteristic, Inamed provided conclusions regarding the modes of failure and whether the characteristic represented a true device failure or an artifact. An artifact is something that may have affected the explanted device prior to laboratory examination (e.g., shipment, excessive handling, autoclaving, method of explantation). Inamed's conclusions were as follows:

- A smooth-edge opening is a failure characteristic that is created by a fold flaw. The mode of failure for a smooth-edge opening suggests that it is a true device failure that occurs over time and it is unlikely caused by external factors (e.g., autoclaving, surgical instruments). Thus, a smooth-edge opening associated with a ruptured or non-ruptured device is indicative of true device failure.

- A sharp-edge opening is the predominant observation for devices reported as ruptured (60% or 80/133). Therefore, most likely, if a device has a sharp-edge opening, it was reported as ruptured. However, not all causes of sharp-edge openings could be determined. Only 18% (20/109) of sharp-edge openings can be linked to damage by surgical instrumentation during implantation or explantation. The mode of failure for the other 82% of sharp-edge openings is not known. Thus, a sharp-edge opening associated with a ruptured or non-ruptured device is indicative of true device failure or the result of an artifact (e.g., surgical damage).

- The failure mode analysis for broken devices is inconclusive based on the state of the devices when they are received by the laboratory. A broken device is a failure characteristic that may be created by a physician's explantation surgical technique or by propagation of a smooth-edge or sharp-edge opening. Thus, a broken device observation associated with a rupture or non-rupture is indicative of true device failure or the result of an artifact (e.g., surgical damage).

- A device surface observation is a characteristic that appears to result from the device being exposed to stress *in vivo* due to placement technique, improper placement, possible mishandling, capsular contracture, etc. This observation is not linked to device failure. Thus, a device surface observation associated with a ruptured or non-ruptured device is the result of an artifact (e.g., surgical technique).

- A gel-related observation is a characteristic not linked to device failure. Because air can permeate through the shell, some devices may have some air inside the devices. This observation can be created by applying excessive stress to the device prior to implantation or during explantation. Thus, a gel-related observation associated with a ruptured or non-ruptured device is the result of an artifact (e.g., surgical technique).

- A functional observation is a characteristic where there is no observed device failure, device surface observation, nor gel-related observation confirmed by the laboratory. A common example is a device returned for bubbles in the gel but the bubbles were determined to be acceptable in size or quantity based on device specifications. Another example is a device that was removed due to a complaint of capsular contracture, but the device itself is found to be intact and functional. Thus, a functional observation associated with a ruptured or non-ruptured device is the result of an artifact.

FDA does not necessarily agree with Inamed regarding their determination of which characteristics are a device failure versus as result of an artifact. We believe that any problems associated with the device and its intended use, including its surgical technique, should be considered a device failure (e.g., excess stress applied during implantation or explantation, cutting the device in order to be able to remove it, capsular contracture). Likewise, artifacts should be limited to problems caused after explantation (e.g., shipment, autoclaving).

Inamed considers these retrieval study findings to be inconclusive to determine any specific steps to take with regard to improvements in device manufacturing, device design, surgical technique, or labeling. However, Inamed noted that Style 153 had a higher rate of sharp-edge openings posteriorly, as compared to other styles, but that no statistical difference was noted in the mechanical properties between ruptured and non-ruptured implants. Inamed will continue to monitor the rate of sharp-edge openings on Style 153 devices, irrespective of the posterior vs. anterior issue. In addition, Inamed stated that they will continue to evaluate the possible causes of sharp-edge openings for all styles.

6. PRECLINICAL - SHELF LIFE

The shelf life testing for silicone gel breast implants is comprised of device and package testing. The mechanical testing included shell ultimate break force, shell ultimate elongation, shell tensile set, patch joint integrity, and gel cohesion. Additionally, Style 153 implants were also tested for bladder joint integrity, which is the only style with that design. Packaging testing included visual inspection, thermoform peel force, and dye penetration. Prior to aging and testing, all samples were subjected to a shipping simulation as per ASTM D4169.

Inamed provided a combination of accelerated and real-time shelf life testing on their silicone gel product. Inamed also provided a combination of accelerated and real-time shelf life testing on their approved saline product to validate the accelerated model out to a 2-year timepoint.

Based on all shelf life data provided, Inamed supported a 2.5-year expiration date on their package label (2 years real time + ½ year accelerated).

7. CLINICAL – STATISTICAL ANALYSIS OF CORE STUDY

The following is the statistical analysis for the Core Study.

Safety Assessment – Descriptive Statistics on Complications

1. Inamed assessed safety by recording 34 types of *medical* complications and unanticipated *device adverse events.* For each medical complication, Inamed provided:

    - Kaplan-Meier analysis
    - prevalence
    - incidence
    - method for resolution
    - time to resolution.

    Important: *The 34 medical complications are not exclusive. In other words, a patient may experience more than one complication and will be included in the risk for all other complications.*

2. *Implant rupture was* assessed by:

    - Kaplan-Meier analysis
    - prevalence
    - incidence
    - method for resolution
    - frequency distribution of method of rupture detection/suspicion
    - frequency distribution/classification of confirmed/unconfirmed rupture status.

3. *Reoperations* were described by:

    - Kaplan-Meier analysis
    - number of reoperations per patient
    - intraoperative complications during reoperation
    - primary reason for operation
    - primary procedure performed
    - number of procedures performed per reoperation
    - types of procedures performed during reoperation

4. *Implant replacement/removal* was assessed by:

    - Kaplan-Meier analysis on the time to first occurrence
    - frequency distribution of the primary reasons for implant replacement/removal
    - frequency distribution of the physician evaluation of the explanted devices
    - frequency distribution of the type of replacement device
    - frequency distribution of the size of replacement device.

Safety Assessment – Risk Factor Analysis

Inamed performed a Cox proportional hazards regression to examine whether specific patient, device, and surgical characteristics are risk factors associated with critical clinical outcomes. The following 5 critical outcomes were examined:

- reoperation
- implant replacement/removal
- implant rupture
- capsular contracture
- infection

Seven patient, device, and surgical characteristics were selected as potential risk factors:

- patient age (≤40 versus >40)
- pocket irrigation – antibiotic (yes versus no)
- pocket irrigation – betadine (yes versus no)
- implant placement (submuscular versus other)
- incision site (periareolar vs. inframammary vs. axillary vs. other)
- device texture (smooth vs. textured)
- device shape (round vs. shaped).

Effectiveness Assessment

Effectiveness was assessed through measurements of pre- and post-surgery *breast size*, level of *satisfaction with the outcome* and *quality of life* measurements prior to the implantation and then at 1, 2, 4, 6, 8, and 10 years post-implant. The quality of life measure was assessed through a questionnaire covering a variety of parameters including *general health*, *depression screen*, *self-esteem*, and *body image*.

A repeated-measures ANOVA was conducted for measures involving interval-level data. If the overall repeated measures analysis was significant, post-hoc comparisons using Tukey's multiple comparisons technique were conducted to determine which specific means differed.

For dichotomous measures, a Cochran-Mantel-Haenszel statistic was computed with Scheffe's correction for multiple comparisons. For the quality of life analysis, the Type I error was adjusted by a Bonferroni correction.

Sample Sizes

The sample sizes were determined with the objective of achieving a pre-determined precision (confidence interval sizes) for the relevant endpoints, since no comparisons to a control group were to be made. Inamed followed the FDA breast implant guidance to determine the sample sizes.

Comments

1. Only descriptive statistical methods were used to assess medical complications and effectiveness in this submission. There are no claims or targets to be reached. The statistical results should help the reviewers to form an opinion with respect to the safety and effectiveness of the implants and to weigh their risks and benefits.

2. There was no control group in the studies and there were no pre-defined clinically meaningful differences to be detected for the adverse event rates.

3. Because the studies are descriptive rather than inferential, the sample sizes just determine the length of the confidence intervals for the variables of interest. If the reviewers are satisfied with the length (precision) of the confidence intervals, then the sample sizes are adequate.

4. Many investigators located at several sites participated in each study. However, a statistical justification for pooling data across sites is difficult due to the low number of patients per investigator or site. Inamed provided a clinical justification for pooling the sites.

5. Inamed provided tables with demographic profiles of the study populations. However, the demographic variables were not used as covariates in the analysis of the adverse event rates.

6. The onset of most complications, such as capsular contracture or infection, cannot be determined precisely. In some instances (e.g., implant rupture), there is no way to know the exact day of occurrence. FDA will know that it occurred before the follow-up time or before an MRI was performed but not when the event actually had occurred. That means that the time for rupture is "censored on the left" (we would know that it had occurred before time *t*). Consequently, FDA suggested that sponsors take the censoring process into account and make corrections to the Kaplan Meier analysis (Turnbull, B.W., Nonparametric Estimation of a Survivorship Function with Doubly Censored Data, Journal of the American Statistical Association, Vol. 69, Number 345,169–173, 1974.).

   Inamed claimed that the only adverse event for which the time of onset is ill defined is silent (i.e., asymptomatic) rupture and then provided the silent rupture numbers below.

	Confirmed Ruptures	Suspected Ruptures
Augmentation	2	3
Reconstruction	8	5
Revision	5	3

   Additionally, Inamed stated that the time to first occurrence of all complications (except for silent rupture) is defined as the difference (in days) between the day of onset reported by the physician for a first occurrence of the complication and the date of surgery. The time of onset for silent rupture was estimated as halfway back from the date of the patient's reoperation/explant or diagnostic test to the last day the implant was known to be intact (i.e., day of implantation).

7. According to Inamed's Kaplan-Meier calculations, some patients discontinued the follow-up very early in the study (one patient discontinued on the first day, a second patient discontinued on the second day, a third patient discontinued on the sixth day and so on). Inamed had no explanation for the early drop-outs but stated that they are reported. Inamed added that several measures were taken to minimize the number of patients who were lost to follow-up.

8. Inamed confirmed that a patient who experienced a complication was returned to the "pool" of candidates to experience other complications, when performing the Kaplan-Meier analysis. This procedure will avoid the problem of *competing risks* in the analysis.

9. Inamed defined incidence as the number of *new* patients/implants experiencing the complication for the first time during each visit interval. Prevalence was defined as the number of patients/implants that are *currently* experiencing the complication during each visit interval.

10. Inamed did not provide the correlation among the adverse events (correlation matrix). If the adverse events are positively correlated, fewer patients will be affected, although the ones affected will tend to have more than one adverse event.

11. Inamed performed analyses of effectiveness outcomes using quality of life measures. It was concluded that the sample of women participating in the clinical studies had higher baseline quality of life scores than the general population. The majority of patients in the sample reported being satisfied with their implant surgery at all follow-up visits. However, there was no control group to compare the results.

12. The number of implants not affected by adverse events (see Kaplan-Meier tables) is not always twice the number of patients not affected by adverse events. The number of remaining implants not affected by a complication may be greater than twice the number of patients not affected by a complication because a patient may be affected in only one breast. In addition, the number of remaining implants not affected by a complication may be smaller than twice the number of remaining patients not affected by a complication because some patients have only one-side implants.

13. In the Reconstruction study, only 59% of patients have reached the 3-year follow-up visit. For those cases in which there was no adverse event between the second and third year, the confidence interval for the cumulative risk at the third year remained the same as the confidence interval for the second year. This happened because Inamed used SAS Proc Lifetest, which gives the Standard Errors computed using Greenwood's formula. The problem with Greenwood's formula is that the interval remains the same for the last interval with an event onward, even if patients are censored after the last interval with an event. Although the rate itself should be the same, the confidence interval at the third year should be larger because the estimate is based on a smaller sample.

    Because a large proportion of patients did not have the third year follow-up in the Reconstruction study, FDA asked Inamed to recalculate the confidence intervals using Peto's formula.

    Greenwood's formula : $$se(s(x)) = s(x)\left[\sum_{j=0}^{x}\frac{d_j}{l_j'(l_j'-d_j)}\right]^{1/2}$$

    Peto's formula: $$se(s(x)) = \left[\frac{s(x)(1-s(x))}{l_{x+1}/s(x)}\right]^{1/2} = s(x)\left[\frac{(1-s(x))}{l_{x+1}}\right]^{1/2}$$

    se: standard error
    1-s(x): estimated cumulative event probability

d_j : # of events at interval j

l_{x+1} : number of patients entering interval $x+1$

Accordingly, Inamed calculated new confidence interval's (Peto's) for the Kaplan-Meier rates in order to account for the fact that a large proportion of the patients in this cohort had not reached the 3-year follow-up time point. The new confidence intervals provided by Inamed are much wider, reflecting the reduced sample size at the 3-year timepoint.

8. CLINICAL – LITERATURE REVIEW

There are several safety issues that are not fully addressed through the data collected in the prospective clinical studies provided in support of this PMA or for which no data were collected in the prospective studies. Thus, a literature review was completed by both Inamed and FDA on the following issues as they related to breast implants:

- cancer and benign breast disease
- connective tissue disease (CTD) including fibromyalgia
- device failure (silent rupture and gel migration)
- mammography issues (interference and device rupture)
- neurological disease
- breast feeding (ability to breast feed)
- reproductive issues
- offspring issues (safety of milk to breast feed and 2nd generation effects).

Inamed's literature search consisted of using MedLine to search for "breast implants" and "silicones" between 1991 and November 2002, as this post-dates the time period covered for submission of their saline-filled breast implant. Inamed selected English language publications only but included foreign studies when published in English. Inamed searched for randomized controlled trials, clinical studies, reviews, and meta-analysis. Inamed further searched review articles for relevant articles that were not identified in their MedLine search. Inamed's inclusion and exclusion criteria for studies were not specifically stated, but the publications that they identified and reviewed were comprehensive.

Inamed focused on silicone gel-filled implants, excluding reports of studies which focused on other silicone implants, silicone injections, exclusively saline-filled breast implants, double lumen breast implants with an unspecified fill, polyurethane foam-covered implants, or other non-silicone gel-filled breast implants.

FDA also performed a literature search. This search covered new publications after the Institute of Medicine Review on Silicone Breast Implants was completed in the summer of 1999. The areas covered by the FDA search were those bulleted above. In some cases, FDA performed additional searches using PubMed when we were aware of articles that were not reviewed by Inamed and did not appear in the original search.

Below is a review of each of the safety issues bulleted above.

Cancer and Benign Breast Disease

The studies cited by Inamed and the literature, in general, are consistent in not finding an increase in breast cancer in women with breast implants compared to either a comparison population of women seeking other types of plastic surgery or the population at large. The risk of breast cancer is neither increased nor reduced in women with breast implants.[1]

Another cancer that is of particular interest is multiple myeloma. The focus on multiple myeloma grew out of an NCI publication that reported plasmacytoma induction with silicone gel in genetically susceptible mice.[2] Rabkin, et al.[3] report that women under age 45 with breast implants represent an excess in multiple myeloma,(for that age group) based on preliminary results from the National Cancer Institute's multiple myeloma registry. Karlson, et al.[4] reported that there was no laboratory evidence for an increase in monoclonal gammopathy of undetermined origin (MGUS), a potential precursor for some cases of multiple myeloma, in women with breast implants. The clinical significance of MGUS as a predictor for multiple myeloma is not certain. The issue of multiple myeloma or MGUS and silicone breast implants is unresolved. Other studies that examined several cancers (either by linkage studies or cohort studies) did not find excesses in multiple myeloma in women with implants.[5,6,7,8] It should be noted that these studies had different comparison groups and employed different methodologies. Because the studies are small, multiple myeloma rare, and the results inconsistent, the evidence for an association between multiple myeloma or MGUS and silicone breast implants is inconclusive.

Inamed identifies some cancers with higher prevalences in women with breast implants: lung, cervical, vulvar, leukemias, brain, and respiratory.[6,7,8] The increase in leukemia in two studies[6,8] might be attributed to chance alone since there were small numbers of cases and a variety of types described that would not be consistent with a single etiology (silicone implants). Although excesses of cervical or vulvar cancers might be explained by uncontrolled factors attributed to lifestyle, the excess in respiratory and brain cancers are more difficult to explain.[6] The increase in respiratory cancers was largely due to lung cancer and the increase in brain cancers was due to glioblastoma multiforme. The finding of excesses in lung (or respiratory), cervical, vulvar, and leukemia have been reported in more than one study.[6,7,8] These findings are difficult to interpret,[9] and further research is needed to clarify this issue.

Connective Tissue Disease (CTD) including Fibromyalgia

Since the Institute of Medicine's conclusions in 1999 of insufficient evidence to support an association of silicone breast implants with CTD or with atypical CTD, there have been no studies in the published literature to date which suggest an association of breast implants with a specific CTD. There have been a few significant studies published since the IOM report that relate to this issue and which are summarized below.

Kjoller, et al.[10] published a retrospective case-control study conducted from 1977 to 1994 of the prevalence of CTD conditions in women with cosmetic implants and without implants in 8 of 27 plastic surgery clinics in Denmark, comparing them to that reported for hospitalized patients in the Danish National Registry of Patients. The authors found no excess of definite CTD in the implant cohort. For unspecified rheumatism, statistically significant excesses were observed for both the implant and control cohorts when compared with national rates.

Englert, et al.[11] reported a population-based retrospective case-control study to determine the incidence and/or prevalence of autoimmune and CTD in female residents of Sydney, Australia in women with augmentation mammoplasty compared with females with non-silicone associated plastic surgery between 1979 and 1983. There was no difference in the occurrence of CTD or CTD-related parameters (such as carpal tunnel syndrome, digital vasospasm, sicca symptoms, tendonitis, livedo reticularis, abnormal nailfold capillaroscopy), thyroid disorders, fibromyalgia, or multiple sclerosis between cohorts. Axillary adenopathy and low titre positive antinuclear antibody (ANA) occurred with significantly greater frequency in the cases. Higher titres of ANA, which is clinically more significant than low titre ANA, were not significantly different between the groups. Note that this reference was not provided and not included in the sponsor's PMA; however, an earlier publication by the author was included.

Fryzek, et al.[12] published a retrospective cohort study of 28 self-reported symptoms (ranging from painful joints to constipation) in women with cosmetic breast implants and with cosmetic breast reduction surgery between 1969 and 1996 taken from the Swedish Inpatient Registry. Questionnaire completion rates were 65% and 72% for these respective cohorts. Symptoms were more frequently reported by the women with implants compared to those with breast reduction. This study was funded by Dow-Corning Corporation.

On the issue of a new or undifferentiated CTD associated with breast implants, Laing, et al.[13] published a retrospective case-control study of women diagnosed with undifferentiated connective tissue disease (UCTD) between 1980 and 1992 and exposures to silicone-containing and non-silicone-containing medical devices in Michigan and Ohio. 201 UCTD cases and 2,095 controls selected by random digit dialing were selected. When all silicone containing devices (including shunts and catheters) are considered, a significant association was observed (odds ratio, OR, 2.81); however, the OR for exposure to breast implants was increased but not significantly (OR 2.22), even when multiple adjustments were made. This study was funded, in part, by Dow-Corning Corporation.

On the issue of fibromyalgia (FM) and breast implants, Wolfe, et al.[14] reported a case-control study of patients seen at the Arthritis Research Center at the University of Kansas, School of Medicine between 1991 and 1994. 464 patients with RA, 508 with FM, and 261 with osteoarthritis (OA) were compared to 503 randomly selected controls. No association between pre-disease silicone filled breast implantation and FM was detected regardless of the control group used (OR 1.22). No association was found with RA as well (OR 1.66) compared to the combined control groups. The lead author for this report has been retained as an expert witness by Dow Chemical.

On the issue of FM, Lai, et al.[15] examined the medical records in a single rheumatology practice in Atlanta of 2500 women seen between 1986 and 1992 in this uncontrolled retrospective cohort study. Univariate and multivariate regression analyses indicated significant associations between FM and hypermobility (OR 2.2), and between hypermobility and breast implantation (OR 1.8), but no association was found between breast implantation and subsequent FM (OR 0.74). Brown, et al.[16] evaluated self-reported FM diagnosis in women with and without ruptured silicone breast implants in this uncontrolled retrospective cohort study. Women with extra-capsular gel noted on MRI examination were twice as likely to report a diagnosis of FM (OR 2.7) compared to women without extracapsular gel noted on MRI.

A reference published by Janowsky, et al.[17] and not cited by Inamed Corporation in their PMA, summarized the previously published data on CTD and breast implants in a meta-analysis. No associations were found between breast implants in general, or silicone gel-filled breast implants specifically, and individual CTD's, all definite CTD's combined, or other rheumatic or autoimmune conditions.

With respect to autoantibody development following breast implantation, Karlson, et al.[18] studied women from the prospective cohort of the Nurse's Health Study. The authors randomly selected 200 women who had been exposed to silicone breast implants and who never reported a CTD during 14 years of follow-up and 500 age-matched, nonexposed women, including some women with definite CTD, some with at least one symptom of a CTD, and healthy controls. There were no statistically significantly higher levels of autoantibodies in women with implants compared to healthy controls with the exception of anti-ssDNA antibodies, which has an unknown clinical relevance. Another study by Karlson, et al.[19] evaluated women selected from the run-in phase of the Women's Health Study for autoantibodies and serologic factors suggesting immune activation. The authors found isolated decreased complement levels C3 and C4 in women with breast implants compared to women without breast implants and to women with diabetes, without corresponding elevations in antinuclear antibody levels or of elevated monoclonal immunoglobulin levels, suggesting a spurious finding.

In summary, the published literature following the IOM report of 1999 does not support an association of breast implants and CTD. This literature cannot completely address rare diseases, such as individual CTDs. One reference suggests there may be a subset of women who may be susceptible to having FM. However, the characteristics that define this subset have not been defined, and these findings have not been confirmed.

Device Failure (Silent Rupture and Gel Migration)

While Inamed's Table 7 (Attachment 18 of original PMA P020056) identifies all published references that summarize rupture rates, there are two additional studies[20,21] in which MRI screening for rupture was performed. In these studies of implants from a variety of manufacturers and of varying ages, by implant rupture rates of 26% and 55% were reported, respectively, for implants of an average age of 10 years or more.

In their review, Inamed provided no discussion of the significance of implant rupture. Based on the literature, the rupture rate for silicone gel breast implants increases with implant age, and rupture may be silent or asymptomatic. Because implant age is a factor in rupture, it is not clear whether later generations of implants have improved with respect to rupture – since these implants have not achieved the age of earlier generations.

One consequence of implant rupture is gel migration. FDA was unable to find any studies on distant gel migration with an estimate of how frequently this serious problem occurs. However, there are several studies that report that, in some cases, there is gel migration outside of the fibrous scar capsule (extracapsular rupture) following rupture.[22,23,24] Cases of distant migration of gel to breast, axillary lymph nodes, abdomen, groin, arms, and fingers have been reported,[23] some with serious consequences and deformities (e.g., extensive migratory granuloma formation and contracture, and scarring from gel extrusion and ulceration) described as a result of gel migration.[25] Inamed also reported on the results of a physician survey in which 5 cases of

migration were reported out of 114,617 silicone gel breast implants representing an incidence rate of 0.004%.[26]

Mammography Issues

There are two mammography issues associated with breast implants: (1) interference of breast implants with mammography and (2) breast implant rupture during mammography.

As described above, women with breast implants are at the same risk for breast cancer as other women. Silicone gel implants may interfere with mammographic detection of potentially curable breast cancer in a number of ways outlined by Inamed: (1) silicone gel is radiodense and obscures part of the breast; (2) implants decrease compressibility of the breast; (3) implants compress adjacent soft tissue leading to increased density and poorer radiographic images; and (4) implants decrease the measurable area for mammography. Also, capsular contracture, which may affect up to 70% of women with silicone gel implants to some degree, may distort the breast making compression extremely difficult and potentially painful.

The possibility that implants may delay cancer detection is of concern. Research results are inconsistent, with some studies finding a delay in detection,[27] and others suggesting that there is no delay.[28] In a study by Cahan, et al.[28], there was no difference in tumor size, axillary lymph node involvement, or histopathology in women with implants compared to nonaugmented patients or breast cancer patients from surveillance, epidemiology, and end results data (SEER). However, there was a difference in preferred treatment options with total mastectomy preferred over breast-preserving procedures in women with implants. In another study by Brinton, et al.,[1] breast cancer was detected at a later stage in women with breast implants, but there was no significant difference in mortality between women with implants and the comparison group with respect to breast cancer.

Some radiologists conclude that standard mammographic views with conventional screen-film mammography are inadequate for women with breast implants[29] and that even the use of additional modified compression views[30] offers only a moderate improvement in cancer detection for these patients. From 22 to 83% of breast tissue may be obscured by silicone gel implants.[31] In some women with capsular contracture, mammographic imaging may not be possible and adjunct methods of cancer detection will be necessary.

Several reports in the literature have described implant rupture during mammography.[32,33,34,35,36,37,38,39, 40,41] In these cases, women felt pain during or soon after mammography, heard, or felt implants rupturing during compression, or experienced changes in the breast shape or texture, and subsequently were found to have implant ruptures. It is not clear whether compression ruptures implants, ruptures the scar capsule and converts intracapsular rupture into extracapsular rupture, or both.

Neurological Disease

There are few studies that examine potential neurologic effects on women with breast implants. Early case reports suggested "a motor neuron disease syndrome" or "multiple sclerosis – like" disease in women with breast implants. A case-control study examined selected chronic diseases using an insurance claims database and there was a positive association between Meniere's syndrome or progressive neuropathy and implants.[42] A subsequent case-control study on women

with Meniere's or sensorineural hearing loss did not confirm an increase in implant exposure in the cases.[43]

A Swedish population based cohort study compared the occurrence of neurologic diagnoses in hospital discharge records for women with breast implants compared to women with breast reduction surgery or to the population at large.[44] There was not a statistically significant increase in neurological disorders, including multiple sclerosis, amyotrophic lateral sclerosis, and Meniere's disease. However, there was a statistically significant difference in "all neurologic diseases listed" for cosmetic breast implants and, overall, rates for women with implants and for women with breast reduction surgery tended to be higher than for Swedish women at large. A similar study used the Danish National Register of patients.[45] Like the previous study, both women with breast implants and breast reduction surgery had increased rates of hospitalization for neurologic disease overall. A specific neurologic entity did not emerge in either of these studies. These studies are of hospital discharge records so will reflect the most severe neurologic disease. Milder neurologic disease or symptoms would not have been assessed. These studies are limited in that rare neurological diseases cannot completely be addressed by epidemiology studies.

Breast Feeding (Ability to Breast Feed)

Breast feeding issues include safety of the milk as well as the ability of mothers to breast feed with breast implants. This section focuses on the ability of mothers to nurse with breast implants. The safety of the milk for breast feeding children is discussed in the **Offspring Issues** section below.

There are several studies that describe nursing problems for women with implants.[46,47,48,49] In one such study, women with a history of breast surgery were five-times more likely to have lactational insufficiency than were those without breast surgery history.[48] Another study described lactation after augmentation mammoplasty and reported that 64% of augmented women who nursed infants had lactational insufficiency compared to less than 7% in non-augmented women.[46] In summary, while no study indicated a qualitative difference in breast milk from women with implants, women with breast implants, or breast surgery in general, were less likely to successfully breast feed an infant.

Another issue is women who do not attempt to breast feed because of concern over implant rupture, pain due to capsular contracture, or concern over the potential for silicone in breast milk. Similarly, women reported not attempting nursing their infants because of concerns in a survey of women with saline implants by Strom, et al.[50] The Core Study protocol did not collect information on women's reason(s) for not breast feeding.

Reproductive Issues

There is a potential concern about the effect of breast implant on female reproduction, including infertility and spontaneous abortion. Offspring issues are discussed separately in the **Offspring Issues** section below.

In a published report, Dow Corning Corporation described reproductive and developmental toxicity studies of silicone gel in rats and rabbits.[51] This study focused on fertility, parturition, neonatal viability, growth of the newborn, and reproductive performance in rats and rabbits using

subcutaneous implants of silicone gel. There were no statistically significant differences between control and animals treated with from 3-30 ml/kg of gel Q7-2159A. A report by Dow Corning described studies performed on octamethylcyclotetrasiloxane (D4), a siloxane component found in silicone gel breast implants.[52] This study examined effects of inhaled D4 on female and male Sprague-Dawley rats. Maternal exposure resulted in a statistically significant decrease in mean live litter size and an increased incidence of dystocia. Dow-Corning concludes that the exposure effects occur only at exposure concentrations that greatly exceed typical workplace or consumer exposure. Consequently, they do not believe the results represent a substantial risk to health. Also, note the route of exposure for these studies is inhalation.

Offspring Issues

Offspring issues include the safety of the milk for breast feeding children and the teratogenic effects of silicones and other chemicals in breast implants.

Although breast-feeding is considered to be the ideal way for feeding most infants, nursing is contraindicated in maternal exposures to certain drugs, infections, or chemicals.[53] Several concerns have been raised as to whether or not silicone-filled breast implants pose a danger for breast-fed infants. One potential risk arises from leakage of silicone (or another substance) into breast milk resulting in direct toxicity or an abnormal immunologic response in the infant. Another possible concern is indirect exposure from passive transfer of maternal antibodies that have developed in response to silicone. Lastly, transplacental or transglandular exposure to silicone in these infants is feasible.[54] However, several scientific organizations have concluded that development of CTD is not linked to silicone-filled breast implants[55,56] and that breast-feeding is not contraindicated for mothers with silicone breast implants.[53,57,58]

FDA reviewed the published English literature and material provided by Inamed in an attempt to determine the potential risk of silicone exposure to pediatric patients, including offspring of women with such implants. Non-breast implant information was included in this section because the breast implant information on this topic was extremely limited and FDA believed that any information regarding pediatric implants, especially any autoimmune reactions, could be informative.

Published Literature Submitted by Inamed

For this review, the literature regarding silicone exposure in children is divided into clinical studies, exploration of mechanism for silicone effect, and attempts to measure silicone exposure. Case reports describing potential CTD and epidemiological studies encompass the majority of clinical studies. Measurements of antibody (anti-silicone or autoantibody) or macrophage activation comprise the studies exploring potential pathophysiology. Lastly, silicone exposure is quantified from levels of silicon or silicone in breast milk or tissues.

Inamed submitted fourteen case reports of children with clinical manifestations suggestive of CTD. Teuber and Gershwin[59] (1994) described two pediatric patients (female, age 2 8/12 and 9 years) with joint symptoms and positive ANA titers. The mothers of both patients had silicone breast implants with evidence of rupture and had breast-fed their children for 3 months. Additionally, both women developed joint symptoms and positive ANA titers following receipt of breast implants. Gedalia, et al.[60] (1995) reported a 6-month-old breast-fed female infant with skin rash and positive Ro/SS-A antibodies. Her mother with silicone breast implants had a similar rash, joint symptoms and positive ANA and Ro/SS-A antibodies.

Levine and Ilowite described a case-series of 11 patients with esophageal dysfunction.[61] In this report, esophageal manometry, biopsy and antibody testing was performed in children with abdominal pain with and without exposure to maternal silicone breast implants. Eight children were breast-fed, while three were bottle-fed. Although differences in esophageal motility were noted between 8 silicone implant-exposed breast fed patients and 17 controls, no significant difference between the 3 bottle fed children and controls were noted. Presence of positive autoantibodies was not statistically different between silicone implant-exposed breast fed children, bottle-fed children, or controls. Biopsies of patients with abnormal manometry were not consistent with scleroderma. Additionally, silicone crystals were absent from esophageal biopsies in all groups. Levels of autoantibodies did not correlate with esophageal abnormalities. Maternal autoantibodies were not reported in the study. Subsequently, Levine, et al. published a follow-up study of these 11 patients. Although esophageal manometry (LES and UES pressures) did not change, 7/11 children had subjective improvement in clinical symptoms. Repeat esophageal biopsies in 10 patients did not reveal any evidence of scleroderma.[62] A highly selected referral population served as the population for case assignment. Only 11 patients from the original 67 referred to the clinic were studied, the 8 silicone implant-exposed breast fed patients were from 4 families and one investigator served on the board of Children Affected by Toxic Substances.[63] Ironically, injectable silicone has been used to treat localized scleroderma[64] Animal models have failed to reproduce the findings of Levine and Ilowite.[65] Rasco, et al. were unable to demonstrate silicone accumulation in esophagi of silicone implant-exposed breast fed rat progeny or those directly exposed to silicone.[66] Frondoza, et al. found that silicone administration to mice did not result in the development of a scleroderma-like syndrome.[67] Case reports can be useful in the identification of potential issues or concerns associated with a potential exposure, but they cannot be used to evaluate a casual relationship between the exposure and the reported outcomes due to the high degree of data uncertainty.

Three large retrospective cohort studies of esophageal disorders, rheumatic disease, and congenital malformations did not demonstrate an increased risk for these conditions in children born to mothers with silicone breast implants compared to a control group of women who underwent plastic surgery.[68,69,70] Additionally, compared with children born after implant surgery, children born before maternal silicone breast implants had a significant increase in congenital malformations and perinatal death.[70] Moreover, excess in hospitalization rates for esophageal conditions was observed in children born before and after maternal silicone breast implants compared with controls.[69] These studies are limited somewhat by retrospective nature. Numbers are insufficient to detect a rare event.

The detection and methods of measuring anti-silicone antibodies in these studies has not been validated or reproduced. Some investigators have failed to find any evidence of an increase in silicone antibodies in women with breast implants.[71,72]

Smalley, et al. described a positive T-cell antibody response to silica among offspring of silicone breast implants recipients (with negative findings in controls).[73] Maternal antibodies to silica were also positive. Correlation with clinical findings was not performed. Not all children were breast-fed.

Levine, et al. did not find a difference between development of autoantibodies in children born to women with (n = 80) and without (n = 42) silicone breast implants. Control women were

randomly selected from Gastroenterology or Rheumatology clinics. Autoantibodies in this study consisted of antinuclear (ANA), anticentromere, antibodies to nRNP, Sm, SS-A, SS-B, Scl-70, and thyroid, anticollagen, and complement levels. Importantly, clinical symptoms, physical assessment, and esophageal manometry did not correlate with positive autoantibody level(s).[74] Poor study design may account for the inability to draw any conclusions from this latter report. Serum was obtained from only 80/303 children eligible for study in the silicone breast implants group. Half the control mothers carried the diagnosis of fibromyalgia.

There is concern that the presence or development of autoantibodies in children may be linked to later development of autoimmune disease. In a population without reported exposure to silicone breast implants, a follow-up study of children with neonatal lupus (and exposure to maternal anti-SSA/Ro and/or SSB/La antibodies) suggested that occurrence of autoimmune disease in early childhood might be of concern. Fortunately, in this small study of neonatal lupus, an increase in the incidence of systemic rheumatic disease did not occur in the children or in their unaffected siblings compared to ethnic and age-matched controls.[75]

In an attempt to demonstrate that silicone exposure activates macrophages, resulting in release of inflammatory mediators, Levine, et al. measured urinary nitrates (NO_3 and NO_2), Neopterin and esophageal manometry in breast-feeding infants of mothers with (n = 38) and without silicone breast implants (n = 30). Levels of these inflammatory mediators were increased in silicone implant-exposed breast fed children compared with controls ($p < .05$ urinary nitrates, $p < .01$ Neopterin). Moreover, increasing levels of neopterin correlated with severity of esophageal dysfunction ($r = -0.38$, $p < .05$).[76] The study population was a highly selected referral population. Confounding factors such as diet and urinary tract infection may have influenced nitrate or neopterin levels. Epstein criticizes this study for poor study design, misinterpretation of results and lack of disclosure.[77]

Semple, et al. found no differences in silicon levels in breast milk from women with silicone breast implants (n=15) and controls (n=34). Levels of silicon in cow's milk (5 brands) and formula (26 brands) were approximately ten-fold higher than levels in breast milk.[78] Patients with mastitis and exposure to other silicone devices or medications were excluded from study. Breast milk collection, decontamination of lab equipment, and sample preparation was standardized to prevent silicone contamination.

Besides Semple's study, which was submitted by Inamed, few additional studies compare levels of silicone (or silicon) in breast milk and formula. Low levels of organosilicone were found in samples of breast milk from women with silicone breast implants, controls and water blanks. The three groups did not differ significantly in levels of PDMS or equivalent.[79] This study was small (6 samples per group). All the test samples were frozen, while all but one of the control samples was fresh. The report was a "feasibility-methods developmental study that was not performed under GLP.[79] Liau detected similar low levels of silicon in breast milk samples from 2 women with silicone breast implants and one control in a small report.[80] Moreover, Lugowski, et al. found no significant difference between silicon levels in breast milk from nursing women with and without silicone breast implants ($p = .466$). Levels in cow milk formula were a "few orders of magnitude" higher.[81] The ubiquitous nature of silicon, geographic variation in levels, and difficulties inherent in avoiding contamination when measuring silicon levels complicate interpretation and generalization of these small studies. The utility of silicon as a proxy measurement for silicone is also unclear.

Additional Literature Regarding Pediatric Exposure to Silicone

Silicon occurs commonly in nature, accounting for 28 % of the earth's weight, second only to oxygen.[82] Environmental exposure occurs to children from silica in soil, concrete, ceramics and building materials. Tap water, vegetables, grain, rice, and beer contain silicon.[54,82] Nipples used for feeding infant formulas or in breast pumps also contain silicone.

Man-made polymers of silicon form compounds ranging in viscosity form gel to solid commonly termed "Silicone." The most common silicone polymer in medical devices is polydimethylsiloxane (PDMS) with average molecular weight of 24,000.[83]

Medical silicone has been used in the pediatric population for many years. In plastic surgery, silicone is used for facial reconstruction, repair of congenital breast disease,[84,85] testicular prosthesis,[83,86,87] and keloids.[88] Numerous stents containing silicone have been placed to treat vesicoureteral reflux[89,90,91] or tracheal disease.[92] Silicone oil is used in ophthalmology for treatment of detached retinas.[93,94,95] Orbital implants are placed following blowout fractures[96] or reconstruction of orbital wall defects.[97] Silicone mesh promotes healing in burn patients.[98] Silastic patches are used to close abdominal wounds after pediatric liver transplantation,[99] cardiac surgery,[100] or gastroschisis repair.[101] Many intravenous catheters containing silicone are placed in children, particularly in hematology-oncology patients. Liquid silicone is a component of tubing used for hemodialysis, intravenous fluids, and pharmacologic agents.[83]

FDA classifies silicone as GRAS (generally regarded as safe) for oral administration as part of antacids[102] (21 CFR 331.11 L1.2). Simethicone, which contains PDMS, is frequently given to infants and children to treat colic and/or GI upset.[103,104,105,106,107] Despite this broad exposure, FDA's literature search identified only one case report of a complication secondary to simethicone. Pivnick, et al. describes rickets in a 5½ month old infant related to Mylanta (simethicone and alumina).[108] The development of rickets in this case is most likely related to the aluminum, which is a known risk factor for rickets.[109]

Silicone may not be biologically inert. Foreign body reactions occur in pediatric recipients of ophthalmologic stents,[110] intraocular silicone oil,[95] silicone skin expanders,[111] and around intravenous catheters.[112] Genest, et al. describes silicon-rich particles in the tissue capsule of explanted juvenile testicular prosthesis; the material was detected via scanning electron microscopy and electron microprobe studies and is described as "silicon-rich."[113] According to Dewan, et al., use of a peristaltic infusion pump with silicone IV tubing apparently results in administration of silicone particles to children.[114] Complications other than local reactions to medical silicone are described infrequently.

Migration of implants, antibody development, and lupus has been reported in pediatric patients. Migration of material is a concern for other implants in addition to silicone breast implants. Reinberg, et al. prospectively evaluated silicone shedding in 6 pediatric patients after removal or exchange of an artificial sphincter. Silicone was detected in the perisphincteric tissue in 3 patients but not in regional lymph nodes. More sensitive X-ray spectroscopy was not performed.[115] Chronic or acute disease in this small group of patients was not described. Although silastic stents are considered safe and effective, exclusion of CTD or autoantibody formation is not specifically addressed in large reviews of urologic stents.[91]

Bowen, et al. describe an infant who died from pulmonary hypertension associated with a foreign body reaction. Silicon, titanium, and talc were identified in granulomas present in small vessels of the lung. The authors speculated that contamination of IV fluids or migration of catheter fragments resulted in the foreign body reaction.[116] Toti, et al. describes silicon-bearing calcifications in the brain of a child with celiac disease; x-ray spectroscopy detected silica in this case.[117]

Jacobs, et al. reported the long-term outcome in children receiving from silastic tracheal stents.[92] 27/33 patients survived (follow-up 4 months to 14 years) and are asymptomatic. Of the six who died, 4 died from potential foreign body reactions (airway or pulmonary hemorrhage, while 2 died from unrelated causes (cardiac failure and one from GI failure). CTD or autoantibody formation was not assessed.

Silicone synovitis has been reported in recipients of patients after implant arthroplasty, despite exclusion of patients with known rheumatoid arthritis. Notably, 3/11 patients with silicone synovitis were adolescents.[118] Additionally, a 16-year-old with scaphoid nonunion developed pain, swelling, and lytic lesions following silicone implant surgery.[119]

Jacobs and Imundo report two silicone implant-exposed children who developed lupus (SLE). One, a 15-year-old boy, 12 years following testicular implantation presented with butterfly rash, proteinuria and pleural effusion, positive ANA and dsDNA and renal biopsy consistent with lupus nephritis. The second, a 10-year-old girl (two years after silicone scleral sponge implant) developed joint symptoms, vasculitic rash, positive dsDNA and renal biopsy finding of lupus.[120]

In contrast, other investigators have not reported problems with orbital or testicular silicone implants. Christmas, et al.[121] retrospectively reviewed records of 120 orbital implants in children over a ten year period. In the 5 patients with silicone implants, no complications occurred. According to a review of silicone gel testicular implants by Lakshmanan in 1997, connective tissue disorders, auto-immunity, and malignancy have not been reported.[83] Similarly, Pidutti and Morales did not find "a specific pattern of disease" in 34 men (including children) who received silicone gel-filled testicular prostheses.[87] The paucity of reports in the medical literature of complications other than local reactions following direct pediatric exposure to medical silicone is reassuring. However, prospective, long-term follow-up of pediatric patients following silicone implants or silicone implant-exposed breast fed patients for emergence of CTD and/or development of autoantibodies has not been performed. Additional adverse outcomes from all pediatric silicone implants from the Manufacturer and User Facility Device Experience (MAUDE) database are reviewed in the **Device Reports – Additional MAUDE Information** section.

Antibodies to silicone elastomers and reactions to ventriculo-peritoneal shunts developed in 2 pediatric patients described by Goldblum, et al.[122] In a study of patients with silicone implants for retinal detachment, Pastor, et al. detected anti-silicone antibodies in 36% of patients (including children) with solid silicone and in 83% of patients with silicone oil.[123] Signs and symptoms of CTD were absent. Similarly, "abnormal immune responses' were detected in 5 childhood recipients of testicular prostheses without evidence of silicosis. None of these patients had positive ANA or RF or clinical symptoms. One young adult patient in this study underwent prosthesis removal secondary to signs and symptoms of "silicone-reactive or adjuvant human disease" with improvement of symptoms. Microscopic examination of the capsule did not reveal

silicone shedding or foreign body granuloma formation.[86] Only a few patients who received implants as children are included in these studies. Follow up studies by other investigators has shown that the anti-silicone antibody is not specific for silicone substrate.[65] The changes in immune response reported in Henderson's study were nonspecific elevations of immune globulins. The detection and methods of measuring anti-silicone antibodies in these studies has not been validated or reproduced.

In a 1997 symposium regarding the immunotoxicity of medical devices, participants concluded that a cause and effect relationship between silicone and immune response did not exist. Silicone did not appear to alter immune competence in test animals, nor did implant materials trigger specific immune responses. Additionally, silicone implant materials did not serve as adjunct to immune response or amplify autoimmune-like disease.[65]

Other Literature

Reports from several scientific organizations have concluded that the breast-feeding is not contraindicated for mothers with silicone breast implants.[53, 57,58] The American Academy of Pediatrics (AAP) Committee on Drugs (COD) "does not feel that the evidence currently justifies classifying silicone implants as a contra-indication to breast feeding."[53] The Independent Review Group, which was charged with "review(ing) the evidence relating to the possible health risks associated with silicone gel breast implants" states, "the published literature to date does not substantiate the claims that there are significant clinically apparent second generation effects in children born to silicone breast implants mothers."[57]

Despite widespread use, an interaction with other drugs is infrequently reported. Silicone in syringes can inactivate surfactant.[124] Silicone oil increased the toxicity of ceftazidime, vancomycin, and ganciclovir[125] but not triamcinolone.[126] Dimethicone did not affect the pharmacokinetics of ketoprofen,[127] digoxin,[128] cimetidine,[129] and ceftibuten.[130]

Conclusion

Scientific evaluation of an association between silicone gel implants and immune-mediated disease in children is limited to few case-reports. These findings have not been confirmed in an animal model. Attempts to elucidate the pathophysiology of a silicone-mediated immune response have been unrevealing or poorly designed. Moreover, both the validity and significance of a positive silicone antibody response is unclear. Larger epidemiological cohort studies have failed to show an increased risk of connective tissue disease, esophageal disorders, or cancer in children of women with silicone breast implants. Several scientific groups, including the Institute of Medicine and the Academy of Pediatrics, also conclude that a second-generation effect of silicone breast implants is unlikely. Therefore, existing data does not support a cause/effect relationship between silicone implants and connective tissue disorders in children. However, available evidence is insufficient to rule out a rare event or subtle effects on children of women with implants.

A prospective, concurrently controlled long-term follow-up study, comparing adverse outcomes in infants and children of women with and without silicone breast implants might identify potential second generation effects. However, this study would need to include a large number of children in each group to detect a statistical difference and the children would need to be followed for at least 18 years. The feasibility of such a study and the likelihood of obtaining useful data with a study of such duration are extremely limited.

The following tables summarize the offspring literature.

- Table 1 - Health Effects of Silicone Implants on Pediatric Patients
- Table 2 - Rheumatologic Complications from Silicone Implants in Children
- Table 3 - Studies of Antibody Responses in Children Exposed to Silicone Implants
- Table 4 - Measurement of Silicone Exposure.

Table 1 - Health Effects of Silicone Implants on Pediatric Patients

Outcome	Citation	Implant Type and Reason	Study Description	Outcome Rate	Control Outcome Rate	Study conclusion
Cancer	Signorello[70]	Silicone Cosmetic	Retrospective Cohort	1/1589 (0.06%)	17/13274 (0.12%)	No increased risk
Congenital Malformations	Kjoller[69]	Silicone, 84% Gel filled Cosmetic	Retrospective Cohort	21/279 (7.5%)	109/2167 (5.0%)	No increased risk
	Kjoller[68]	Silicone gel-filled single or double-lumen, saline, or other type of filler. Cosmetic, reconstruction, revision	Retrospective Cohort	53/748 (7%)	189/3208 (5.9%)	No increased risk
	Signorello[70]	Silicone Cosmetic	Retrospective Cohort	88/1589 (5.5%)	769/13274 (5.79%)	No increased risk
Death	Signorello[70]	Silicone Cosmetic	Retrospective Cohort	5/1589 (0.3%) 11/1589 (0.7%)	35/13274 (0.3%) 81/13274 (0.61%)	Infant death within 7 days of birth. No increased risk. Perinatal, stillborn or infant death within 7 days of birth. No increased risk.
Stillbirth	Signorello[73]	Silicone Cosmetic	Retrospective Cohort	6/1489 (0.4%)	46/13274 (0.35%)	No increased risk
Digestive organs	Kjoller[69]	Silicone, 84% Gel filled Cosmetic	Retrospective Cohort	2/279 (0.7%)	18/2167 (0.8%)	No increased risk
Esophageal Disorder	Kjoller[69]	Silicone, 84% Gel filled Cosmetic	Retrospective Cohort	4/279 (1.4%)	19/2167 (1%)	No increased risk
	Kjoller[68]	Silicone gel-filled single or double-lumen, saline, or other type of filler. Cosmetic, reconstruction, revision	Retrospective Cohort	6/748 (0.8%)	32/3209 (0.99%)	No increased risk
	Signorello[70]	Silicone Cosmetic	Retrospective Cohort	24/1589 (1.5%)	194/13274 (1.5%)	No increased risk
Rheumatic Disease	Kjoller[69]	Silicone, 84% Gel filled Cosmetic	Retrospective Cohort	0/279	2/2167 (0.01%)	No increased risk
	Kjoller[68]	Silicone gel-filled single or double-lumen, saline, or other type of filler. Cosmetic, reconstruction, revision	Retrospective Cohort	2/748 (0.3%)	9/3209 (0.3%)	No increased risk
	Signorello[70]	Silicone Cosmetic	Retrospective Cohort	2/1589 (0.1%)	10/13274 (0.08%)	No increased risk

Note: Table has been modified from Attachment 18: Review of the Published Literature 1991-2002 submitted by Inamed.

Table 2 - Rheumatologic Complications from Silicone Implants in Children

Outcome	Citation	Patient (age)	Time After Implant (yr.)	Implant Type and Reason	Study Description	Results	Symptoms	Comments
Rheumatic Complaints	Tueber[59]	Female 2 8/12		Mother with silicone breast implants	Case Report	+ ANA (- dsDNA)	Joint complaints	
Rheumatic Complaints	Tueber[59]	Female 9	6	Mother with silicone breast implants	Case Report	+ ANA (- dsDNA)	Joint complaints	
?Neonatal Lupus	Gedalia[60]	Female 6 mo	5	Mother with silicone breast implants	Case Report	- ANA (+ Ro/SSA)	Skin Rash	
Scleroderma-like Esophageal Disease	Levine and Ilowite[61]	8 Breast-fed 3 Bottle Mean age = 6		Mother with silicone breast implants	Case- Series	Esophageal Manometry abnormalities. Biopsy negative for scleroderma.	Abdominal pain + emesis, dysphagia	Highly selected referral population
Migration	Capozzi[131]	Female (18 yr.)	3	Silicone Gel (Micromastia)	Case- Report	Migration along soft Tissue Planes	Foreign Body Granuloma	
SLE	Jacobs[120]	Male (15 yr.)	12	Silicone Gel (Cryptorchidism)	Case-Report	Renal Biopsy- Class III/V lupus nephritis	Butterfly rash, pleural effusion & proteinuria	
SLE	Jacobs[120]	Female (10 yr.)	2	Silicone Scleral Sponge (Retinal Detachment)	Case-Report	Renal biopsy- Class II lupus nephritis	Joint symptoms and vascular rash	
Silicone Synovitis	Lanzetta[118]	Male (20 yr.)	3	Partial Scaphoid (Avascular Necrosis)	Case- Report	Intra operative histology confirmed	Pain, Swelling & Weakness	
Silicone Synovitis	Lanzetta[118]	Male (20)	2 2/12	Partial Scaphoid (Scaphoid Fracture)	Case- Report	Intra operative histology confirmed	Pain	
Silicone Synovitis	Lanzetta[118]	Male (21)	3 3/12	Lunate (Kienbock's disease)	Case- Report	Intra operative histology confirmed	Pain & Weakness	
Silicone Synovitis	Peimer[119]	Male (16)	1 4/12	Scaphoid (Scaphoid nonunion)	Case- Report		Pain, swelling & lytic lesions	

Table 3 - Studies of Antibody Responses in Children Exposed to Silicone Implants

Autoimmune	Citation	Patient (age)	Time After Implant (yr.)	Implant Type and Reason	Study Description	ANA	dsDNA	Anti-Ro	Anti-Sm		Comments
SLE	Jacobs[120]	Male (15 yr.)	12	Testicular Silicone Gel (Cryptorchidism)	Case-Report	1:640	1008	-	-		
SLE	Jacobs[120]	Female (10 yr.)	2	Silicone Scleral Sponge (Retinal Detachment)	Case-Report	+	+	-	-		
Rheumatic Complaints	Tueber[59]	Female 2 8/12	N/A	Breast fed from Mother with silicone breast implants	Case Report	+ 1:80	-				
Rheumatic Complaints	Tueber[59]	Female 9	N/A	Breast fed from Mother with silicone breast implants	Case Report	+ 1:160	-	-	-		+ anti-collagen
?Neonatal Lupus	Gedalia[60]	Female 6 mo		Mother with silicone breast implants	Case Report	-	-	+	-		
						ANA/RF	**C4**	**IgA**	**IgE**	**IgM**	**IgG**
Asymtomatic	Henderson[86]	Male (18 yr.)	4	Testicular implant (Cryptorchidism)	Case-Report	-	Normal	Normal	High	Normal	Normal
Asymtomatic	Henderson[86]	Male (16 yr)	1	Testicular implant (Cryptorchidism)	Case-Report	-	Low	Low	Normal	Normal	High
Asymtomatic	Henderson[86]	Male (7 yr.)	4	Testicular implant (Cryptorchidism)	Case-Report	-	Not available	Normal	High	Normal	High
Asymtomatic	Henderson[86]	Male (15 yr.)	2	Testicular implant (Cryptorchidism	Case-Report	-	Normal	Normal	High	Normal	Normal
Asthma	Henderson[86]	Male (24 yr.)	7	Testicular implant (Torsion)	Case-Report	-	Normal	Normal	Normal	Normal	Normal
							Silastic IgG				**Comments**
Antisilicone	Goldblum[122]	Female (9 11/12)	9+	Ventriculoperitoneal (VP) shunt (Myelomenigocele)	Case-Report		+				9 Healthy Adults and 5 Children with VP shunts had (-) IgG
Antisilicone	Goldblum[122]	Female (5 ½)	5+	VP shunt (Hydrocephalus)	Case-Report		+				
Antisiliconc	Pastor[123]	14-72	852 days (202-2,027)	Intraocular Silicone (Retinal Detachment)	Case-Series		+				Only Group antibody levels reported

Table 4 - Measurement of Silicone Exposure

Measurement	Citation	Number	Exclusion	Silicone Breast Implants	Controls	Cow's Milk	Formula	Water	Comment
Mean Silicon Levels (µg/L)	Semple[78]	Women with silicone breast implants (n=15) Controls- Women with Breast Augmentation (n =34)	Breast ca, foam or saline, mastitis, diabetes, silicone meds, injection with silicone-lubricated syringes, other prosthesis	55.45 (+/- 35.81)	41.05 (+/- 31.02)	708.94 Range 666.5-778.3	4402.5		Clear Methodology to prevent contamination
Organosilicones (ppm)	Bejarano[79]	Women with silicone breast implants (n=6) Controls- Women without silicone breast implants (n=6)	Not reported	3.4 (+/- 1.02)	3.62 (+/- 0.85)			2.25 (+/- 1.45)	Unpublished Dow Corning Data (No clear GLP)
Mean Silicon Levels (µg/L)	Lugowski[81]	Women with silicone breast implants (n=60) Controls- Women without silicone breast implants (n=29)	Breast ca & reconstruction, foam, surgical revision, suspected rupture or infection, rheumatoid arthritis, diabetes, other prosthesis, CTD	58.66 (+/- 33.8) Range 17-135	51 (+/- 31) Range 10-171	709	Range* 911- 13,811		Clear Methodology to prevent contamination
Silicon (mg/L)	Liau[80]	Women with silicone breast implants (n=2) Woman without silicone breast implants (n=1)	None	<0.5 mg/L	<0.5 mg/L				Blinded and Independent Laboratory. Detection Limit 0.5 mg/L
Mean Silicon Levels (µg/L)	Tanaka[132]	Healthy Postpartum women (n=38)			Range 75-750				Abstract only (Japanese Study)

*Original Data reported concentration in mg/L for concentrate and ready to feed formula and mg/kg for powder. For representative purposes, concentrations of ready to feed formula were converted to µg/L and reproduced in this table.

9. CLINICAL - SEER STUDY

Manufacturers of breast implants provided a grant to the Fred Hutchinson Cancer Research Center to perform a study of breast implant failure in a cancer cohort. Cancer patients diagnosed in 1983, 1985, 1987, and 1989 were identified through the Surveillance Epidemiology End Results registry (SEER) from three SEER sites (Iowa, San Francisco/Oakland, and Seattle/Puget Sound). Of the 6,563 women identified with early stage cancer and who were less than 65 years of age, and had been treated with mastectomy, 18% (1,159) had breast implants. Of the 1,159 women who had reconstruction with breast implant(s), there was information on the details of the implant for 1,012 women with 1,375 implants. The majority of implants (559) were single lumen silicone gel filled implants (40.7%), closely followed by 505 saline/silicone-gel multilumen (double, triple, or quadruple lumens) implants (36.7%). Sixteen percent (16%) were saline breast implants. The duration for implants that were not removed and for which there were estimates of the length of time they had been in place ranged from less than one month to 136 months with a median duration of 70 months. The median duration of use of implants that had been removed was 12 months (mean: 26 months), with a range from less than one month to 122 months.

The endpoint for the SEER breast implant study was implant removal. The removal rate for any reason for all types of breast implants by KM was 24% at 5 years and 39% at 10 years (445 of the total 1,375 implants were removed).

The removal rate for all types of breast implants was at least 445/1375 (32.4%) overall. There were differences in the removal rate by implant type - silicone gel 162 (28.9%), multilumen 150 (29.7%), and saline 96 (43.2%). The large difference in rates of removal may have been due, in part, to misclassification of some tissue expanders as saline breast implants.

The most common reason for removal was capsular contracture (capsular contracture or contracture + other reason(s)) accounting for 30% of all explantation (130/445). The study authors state that these data support the notion that capsular contracture occurs more frequently with single or multiple lumen silicone-gel containing implants than for saline breast implants. However, while the proportion of implants explanted from the total explanted may vary slightly by type (31.4%, 31.3%, and 25%) for single lumen silicone gel, multilumen, and saline implants, respectively, the proportion explanted because of capsular contracture is similar for the three types (9.1%, 9.3 %, and 10.8%).

The second most common reason for removal was for aesthetic reasons or aesthetic + other reasons. Aesthetic reasons included migration/repositioning, dimpling, asymmetry, contour, or size problems. Removal for aesthetic reasons accounted for 16.2% of all explanted implants. It is interesting that the proportion of implants removed for cosmetic reasons is quite similar for the three types of implants (5.7%, 4.9%, and 5.4% for single lumen silicone gel, multilumen, and saline breast implants, respectively) because it is the conventional wisdom that the silicone gel breast implant provides a better aesthetic effect for women with mastectomies. However, it is likely that only extreme cases of dissatisfaction with the aesthetic effect would end in explantation.

Rupture/leaking/deflation rates for implants were similar regardless of type. It should be noted that only ruptures that resulted in explantation would have been counted. In the event that a

rupture was discovered at the time of explantation for silicone gel or multilumen implants, rather than rupture being the reason for removal, it would not have been counted.

For single lumen silicone gel breast implants, multilumen implants, and saline breast implants, the rupture rate (includes rupture/leak/deflated) was 3.0%, 5.2%, and 4.5%, respectively. By implant type, removal for implant rupture, leakage, or deflation accounted for 10.5% of explantations for silicone gel implants, 17.4% of explantation for multilumen implants, and 10.4% of explantation for saline implants.

Other reasons given for implant removal were healing problems, media related problems (defined as autoimmune disease or symptoms, concern/fear over media reports, or allergic reactions), recurrence of malignancy, and other.

Of the 559 single lumen gel-filled implants, 162 (29%) were removed by 10 years, which includes implants removed as part of planned reconstruction. After 10 years, 397 single lumen gel devices (71%) were still implanted. Of the 143 (25.6%) gel implants removed for reasons other than planned reconstruction, the most common reason for removal was capsular contracture (51 implants; 31.4%). This was followed by aesthetic (32 implants; 19.7%), healing (22 implants; 13.6%), mechanical and other (19 implants, 11.8%), media raised concerns (8 implants; 4.9%), unknown/other (8 implants; 4.9%), and, finally, malignancy (3 implants; 1.9%). Removal for aesthetic reasons included implant migration/repositioning, dimpling, asymmetry, and contour/size problems. Healing related included infection, improper healing, necrosis, bleeding, and rejection of the implant. Mechanical reasons included rupture, leakage, deflation, and injury (accident or puncture). Media raised concerns included autoimmune disease or symptoms, concern or fear/ media reports and allergic reaction. Removal for unknown/other reasons included personal preference, non-implant related infection, muscle structure, and chest wall or mastectomy defect/deformity. Malignancy included recurrent disease.

In summary, these data from a breast cancer cohort indicate that, overall, 18% of women with early stage breast cancer underwent implant mammoplasty. Nearly equal proportions of implants were single lumen silicone gel implants and multilumen saline/silicone gel implants (41% and 37%, respectively) and an additional 16% were saline breast implants. The most common reason for removal of implants was capsular contracture, followed by removal for aesthetic reasons. Rupture/leaking/deflation rates were between 3.0 and 5.2%. Overall, 32% of implants were explanted. These rates for removal are consistent with recently reported reoperation rates for women with breast implants for reconstructive purposes[133] or for cosmetic purposes.[41]

10. CLINICAL - POSTAPPROVAL STUDY PLAN

The purpose of a postapproval study is to collect long-term data on a device. Below is a brief summary of Inamed's proposed postapproval study plan for their Core Study.

Inamed proposes a 2-phase postapproval study. Phase I involves patients in the Core Study continuing with their evaluations as per the current protocol through their 5-year evaluation timepoint. Phase II involves a Post-Approval Survey Study (PASS) for continued follow-up from 6-10 years. More specifically, Phase II involves patients completing a mail survey reporting the status of the implants for selected critical safety outcomes and satisfaction. Patients

will be mailed a survey to complete on their original implant surgery anniversary each year from 6 through 10 years post-implantation. Patients will be asked to sign a PASS informed consent prior to their first survey mailing and a contract IRB will review and approve the PASS study for all patients. It should be noted that the patients in the Core Study signed an informed consent document stating that they would have physician follow-up evaluations through 10 years.

All patients enrolled in the Core Study who have not been discontinued through their 5th year will be asked to participate. Patients who are lost-to-follow-up at 5 years will be contacted in an effort to include these patients.

Inamed proposed that the survey collect the following safety data; however, no specific details were provided:

- breast pain
- capsular contracture
- implant rupture
- reoperation (including implant removal/replacement)
- patient satisfaction.

Inamed proposed the measures below to maximize patient compliance; however, no specific details were provided. The measures include:

- multiple mailing for each annual patient survey
- phone calls to non-responsive patients
- search for missing patients
- future mailing to non-responsive patients
- patient incentive payments.

11. DEVICE REPORTS - MEDWATCH

MedWatch is FDA's device reporting system. MedWatch databases consist of voluntary reports by the public and mandatory medical device reports (MDRs) by manufacturers, importers, distributors (until 2/98), and user facilities. To understand the sources of the data, FDA provides the summary table below which describes each of the MedWatch databases/collection systems.

Database/ Collection System	Description	Reported by
Device Experience Network (DEN)	DEN database serves as a historical database for reports. User facilities are listed under voluntary reporting for the DEN because mandatory requirements for user facility reporting under the SMDA 1990 were not in effect prior to 7/31/96, so user facilities were encouraged to voluntarily report. DEN does not contain device or patient problem codes and cannot be searched on many data fields, including implant and explant dates. DEN uses causative factor codes.	Consumers, health professionals, and user facilities Manufacturers
Manufacturer and User Facility Device	MAUDE is the predominate database used by FDA for evaluation of individual device-related adverse event reports. MAUDE is the only database with implant and explant dates. It also had device and patient problem codes, and manufacturer evaluation and conclusion codes.	Consumers and health professionals Manufacturers,

Database/ Collection System	Description	Reported by
Experience (**MAUDE**)	As a note, DEN and MAUDE may include several report sources for one event. For example, one incident may have been reported as a voluntary report by a consumer, a physician, or an attorney, and reported as a mandatory report by a manufacturer, a user facility, or an importer. The databases will link same reports.	distributors, and importers
Alternative Summary Reporting Program (**ASR**)	ASR database contains manufacturer summary reports submitted on a quarterly basis of approved adverse events (usually adverse events that are well-known in the scientific and medical literature). For breast implants, the adverse events include rupture, leaks, deflation/inflation, wrinkling, capsular contracture, and non-specific complaints. In October 1999, new requirements for the ASR program started. Manufacturers now provide patient and device codes as well as evaluation and conclusion codes for each adverse event. Summary reports do not contain narrative text. Implant and explant data are not captured in ASR.	Manufacturers

FDA performed a search on Inamed silicone gel breast implants through the MedWatch databases: DEN, MAUDE, and ASR. Each database has its unique features in terms of the type of data collected. Also, it should be noted that there may be duplicate reports across the databases. FDA performed a search on all silicone gel breast implants for comparison purposes. Although the time period for each database is different, the overall search time period is 1/1/84 through 6/30/03.

As of 6/30/03, FDA received a total of 134,477 reports across all silicone gel breast implant manufacturers. Of those, 14,414 (11%) were Inamed's silicone gel breast implants. The table below shows the number of reports for each of the databases.

Silicone Gel Breast Implant Reports, 1/1/84–6/30/03		
Database	**Total Reports**	**Inamed Reports**
DEN 1/1/84 – 12/31/97	96,954	7,646 (8%)
MAUDE 1/1/92 – 6/30/03	14,034	913 (6.5%)
ASR 4/1/95 – 6/30/02	23,489	5,855 (25%)
Total	**134,477**	**14,414** (11%)

DEN

With regard to the DEN database (1984-1997), both adverse event reports and the associated "causative factors" reports were recorded. There were 593 causative factors reported by manufacturers on 96,954 adverse event reports associated with silicone gel breast implants. There were 69 causative factors reported on 7,646 adverse event reports by Inamed. The table below summarizes the DEN data for Inamed, including the rates of the top causative factors.

DEN, 1984-1997	
Inamed Adverse Event Reports	
Death	2
Injury	7,514
Malfunction	130
Other	0
Total	**7,646**
Rates of Inamed's Top Causative Factors	
	N=69
Known complication (long-term)	71.0%
Anticipated adverse/allergic reaction	17.4%
Incorrect technique/procedure	7.2%
Use error	2.9%

MAUDE

With regard to the MAUDE database (1/1/92 – 6/30/03), there were 17,523 device problem codes and 41,520 patient problem codes submitted on 14,034 adverse even reports across all manufacturers. There were 1,317 device problem codes and 4,248 patient problem codes submitted on 913 adverse event reports for Inamed. The table below summarizes the MAUDE data for Inamed, including the rates of the top device and patient problems.

MAUDE, 1/1/92 – 6/30/03	
Inamed Adverse Event Reports	
Death	11
Injury	638
Malfunction	104
Other	160
Total	**913**
Rates of Inamed's Top Device Problems	
	N=1317
Explanted	35.4%
Rupture	31.8%
Unknown	20.1%
Migration	3.3%
Device remains implanted	2.2%
Rates of Inamed's Top Patient Problems	
	N=4,248
Surgical procedure	8.6%
Pain	7.5%
Capsular contracture	7.0%
Connective tissue disease	5.6%
Fatigue	5.2%
Unknown	3.5%

Additionally, of the 913 Inamed adverse event reports, 863 had implant and explant dates. Those data indicate that the median implant duration for Inamed implants with associated adverse events reported only to MAUDE was 1.8 years and the average implant duration was 8.9 years.

ASR

With regard to the ASR database, from 1995 through 6/30/02, there were 23,489 adverse event reports submitted across all manufacturers, of which 5,855 (25%) were submitted by Inamed.

In the current ASR program, which allows for more detailed entries, the search timeframe was 10/1/99 through 6/30/02. There were 6,292 device problems submitted across all manufacturers. Inamed submitted a total of 4,244 device problems (67% of total). Inamed's top three reported device problems were "explanted," "device remains implanted [associated with a patient problem]," and "rupture, cause unknown," which comprises ≈92% of the device problems.

With regard to patient problems, there were 6,993 patient problems submitted across all manufacturers. Inamed submitted a total of 5,788 patient problems (83% of total). Inamed's top three reported patient problems were "surgical procedure, repeated," "capsular contracture," and "unknown," which comprises ≈93% of the patient problems.

12. DEVICE REPORTS – ADDITIONAL MAUDE INFORMATION

To obtain additional information to supplement the literature, FDA performed a review of the MAUDE databases for (1) mammography issues associated with breast implant and (2) reproductive and offspring issues with breast implants. These reports are not specific to Inamed's implants but are, instead, for breast implants in general.

Review of Adverse Event Reports on Mammography Issues Associated with Breast Implants

FDA searched the database for product codes for silicone-gel breast implants, saline breast implants, and for mammographic systems. All reports received by the FDA and entered in the MAUDE database by 11/6/02 were included. FDA retrieved 654 adverse event reports for silicone-gel breast implants and 51 adverse event reports for saline breast implants.

When the same event was reported by multiple reporters, we combined events into a single report. The reported adverse event was characterized based on the text of the report and coded as implant rupture (explicit or implicit) and other problems reported. Some reports had multiple problems reported, for instance pain during a previous mammographic procedure and fear of implant rupture during mammography. If there was multiple problems, each report was only reported in one category using a hierarchy of potential rupture, delayed cancer detection, pain, and other.

The implant age was calculated when implantation date and event date or explantation date was given. Breast implant type (silicone-gel or saline (inflatable)) was given for the majority of reports but in several cases reported under the product code for mammography systems, breast implant type was not specifically mentioned. In these cases, when possible, we classified the implant type based on the information in the text.

Of the reports retrieved, 66 mentioned a problem related to breast implants and mammography. Table 1 shows characteristics of patients, implants and reporters for adverse event reports related to breast implants and mammography. The 66 reports were received by FDA between 6/16/92 and10/4/02 for adverse events occurring between 6/72 and 6/02. Mean patient age was 49.9±11.8 years and ranged from 28 to 77 years. The mean implant age, when calculated from implantation to event date or explantation date in 28 reports was 14.5±7.9 years and ranged from 2 to 29 years. Most adverse events were reported to the implant manufacturer or mammography system manufacturer by physicians or patients/consumers. Manufacturers, in turn, reported these adverse events to the FDA.

Table 1. Characteristics of patients and implants in 66 adverse event reports describing problems with implants related to mammography or problems with mammography related to implants.

Patient, Implant, or Report Characteristic		N (%)
Patient Age	20-39 years	8 (12.1%)
	40-59 years	31 (47.0%)
	60+ years	11 (16.7%)
	Not reported	16 (24.2%)
Implant Type	Silicone-gel	49 (72.2%)
	Saline (inflatable implant)	14 (21.2%)
	Not reported	3 (4.5%)
Breast Implant Age	0-9years	9 (13.6%)
	10-19 years	13 (19.7%)
	20 + years	6 (9.1%)
	Not reported	38 (57.6%)
Adverse Event Reporter	Physician	16 (24.3%)
	Patient or consumer	19 (28.8%)
	Nurse	8 (12.2%)
	Risk Manager	7 (10.6%)
	Attorney	2 (3.0%)
	Other, not specified/unknown	14 (21.2%)
Report Dates	Event date: June, 1972 to June, 2002	35 (53.0%)
	Report date: December, 1993 to October, 2002	61 (92.4%)
	Received by FDA: June, 1992 to October, 2002	66 (100.0%)

The majority of reports described a potential rupture occurring during mammography (Table 2). While the nature of the adverse event was ambiguous in some reports in other reports, the reporter explicitly stated that an implant was ruptured during mammography (33/66 reports). An additional 7 reports claimed changes to implants or breast after mammography and implied implant rupture due to mammography but did not explicitly state this. Two reports described implants crushed, albeit not ruptured. In several cases, changes in breast texture were reported after mammography. Breasts either became soft or became hard after mammography.

Table 2. Characterization of 66 adverse event reports describing problems with breast implants related to mammography or with mammography related to breast implants, based on report text.

Adverse Event Characterized		N (%)
Potential Rupture Reported	Explicitly claims implant ruptured during mammography	33 (50.0%)
	Pain or change after mammography with subsequent rupture detected	7 (10.6%)
	Patient had emergency removal of implant after mammography	1 (1.5%)
Other Adverse Events after Mammography	Pain during mammography then distorted implant discovered	2 (3.0%)
	Severe pain during or after mammography	9 (13.6%)
	Soft/hard breast after mammography	3 (4.5%)
Problems Related to Mammography Performance or Interpretation	Delayed detection of cancer attributed to implant	3 (4.5%)
	Could not perform mammography because of capsular contracture	1 (1.5%)
	Concern over potential rupture during mammography or interference with mammography	7 (10.6%)

Other adverse events related to mammography in women with implants included pain during or after mammography. Since pain may occur after mammography for unimplanted women, it is difficult to attribute this to the implant with certainty. In cases where the breast is hard or sore from capsular contracture, it may not be possible to perform mammography because of pain and inability to adequately compress hardened tissue.

Other problems reported were related to mammography performance or interpretation because of implants. This included claims of delayed or missed diagnosis of cancer due to tissue obscured by implants. Other reports described fears of undergoing mammography because of fear of pain, fear of implant rupture, or fear that cancers would not be detected because of tissue obscured by implants.

In summary, both silicone-gel and saline breast implants may rupture during compression for mammography. Additionally, breast implants may interfere with mammography imaging.

Review of Adverse Event Reports on Lactation, Reproductive, and Offspring Issues Associated with Breast Implants

FDA searched the MAUDE database for product codes for silicone-gel breast implants and for saline breast implants. We searched the text of the reports for the words birth defect, child, fetal, fetus, infant, lactating, milk, mother, newborn, nursing, pregnancy, reproduction, teratogenicity, and teratogenic. All reports received by the FDA and entered in the MAUDE database by 12/31/02 were included.

FDA retrieved 215 adverse event reports for silicone-gel breast implants and 36 adverse event reports for saline breast implants that contained at least one of these words. We abstracted information from those reports in which the adverse event(s) was reported to be related to breast implant effects on reproduction. When the same event was reported by multiple reporters, we combined events into a single report. The reported adverse event was characterized based on

coded device or patient problems associated with the report (these are coded as the report is submitted). The report was further characterized by the content of the report text, because not all adverse events reported in the text are coded at the time of entry.

Of the 251 reports that included one of the words we searched for, a total of 130 reports asserted that adverse events related to reproductive issues. The remaining 121 reports had one of the key words but were unrelated to reproductive adverse events.

Table 1 shows characteristics of the 130 reports that had a reproduction related adverse event reported with respect to implant type, report type (death, injury, malfunction, or not specified), reporter, subject of report (mother or child) and report dates. The majority of reports related to reproductive issues were for silicone-gel breast implants with 118 reports for silicone-gel and the remaining 12 for saline breast implants. Only 10 reports included the affected child's age and ranged from <1 year to 25 years with a median age of 7 years.

Table 1. Characteristics of reports submitted to FDA on breast implant adverse events that included adverse event related to reproduction.

Patient, Implant, or Report Characteristics		N (%)
Implant Type	Silicone-Gel	118 (90.8%)
	Saline	12 (9.2%)
Event Type	Death	2 (1.5%)
	Injury	123 (94.6%)
	Malfunction	0 (0%)
	Not specified	5 (5.0%)
Reporter	Attorney	81 (62.3%)
	Patient/consumer	27 (20.8%)
	Family member	13 (10.0%)
	Physician	4 (3.1%)
	Other/unknown	5 (3.8%)
Subject of Report	Child(ren) of mother with breast implant	99 (76.1%)
	Mother with breast implant	17 (13.1%)
	Mother with breast implant and her child(ren)	14 (10.8%)
Report Dates	Event dates: December, 1968 to November, 1998	28 (21.5%)
	Received by FDA: July, 1992 to December, 2002	130 (100.0%)

The most frequently reported adverse event for mothers (9/130) was the inability to nurse an infant, usually because of capsular contracture or breast pain related to the implant or other problems during nursing such as implanted breasts becoming "flat" during nursing (Table 2). There were also 5 reports of either single or multiple spontaneous abortions, miscarriage, or tubal pregnancy in women with implants.

Table 2. Characterization of adverse events reported in MAUDE, 1992-2002.

Reported Problems[1]		N (% of 130)
Children's Problems	Non-specified problems that child or children were harmed by mother's breast implants	86 (66.1%)
	Specific problems, illnesses, in children of mothers with breast implants	23 (17.8%)
	Specified birth defects/deformity in children of mothers with implants	5 (3.8%)
Mother's Problems	Difficulty / inability to nurse	9 (6.9%)
	Abortion/miscarriage/tubal pregnancy	5 (3.8%)
	Chronic illness or fatigue related to implants began during pregnancy	2 (1.5%)
	Miscellaneous[2]	1 (<1%)
Mother and Child[3]	Symptoms and illnesses of mother and child could not be distinguished based on report text	2 (1.5%)

[1]Reported problems are based on characterizing the text of the adverse event report. Total will add up to more than 100% because more than one problem may have been reported. For instance, one report asserted that mother was unable to nurse because of severe capsular contracture and that the child had illness due to mother's implants and another report asserted that mother had stillbirth due to implants and that subsequent child was ill because of implants.
[2]A mother reports a black discharge from nipple during pregnancy.
[3]Numerous reports asserted that both mother and child(ren) were ill as a result of breast implants, but in most reports, it was possible to distinguish between mother's and child's problems. In a few reports, it was not possible to attribute illness to mother or child specifically since they were intermingled.

The majority of reports (86/130, 66.1%) were submitted to breast implant manufacturers asserting non-specific illnesses in children believed to be related to the mother's breast implants (Table 2). These reports provide no information on symptoms or illness in children. The next largest group of reports describes illnesses, symptoms, or problems in children believed to be due to mother's implants (23/130 (17.8%).

For the 23 children in whom adverse events were specified, there was a wide variety of signs, symptoms, and diagnoses reported. The most commonly reported adverse events were gastrointestinal symptoms including choking, dysphagia, gastritis, heartburn, nausea, and spastic colon. Pulmonary/respiratory symptoms, including asthma, and allergies were the next most common groupings of adverse events for these children.

There were five reports that described congenital defects in children of women with implants. All 5 of these reports were from women with silicone-gel breast implants. Three of the congenital defects reports were from a single mother of triplets, all of whom were congenitally deformed.

In summary, there were several reported cases of women who were unable to nurse their offspring, usually because of pain, possibly due to capsular contracture. In addition, several women reported single or multiple spontaneous abortions, miscarriage, or stillbirth that they attributed to the implants. There were five cases of congenital deformities/anomalies reported in which the mother attributed the deformities to her implants. The majority of reports on adverse events in children did not specify the illness. In the 23 reports in which specific adverse events

were reported in children, the most common were related to gastrointestinal tract, allergies, pulmonary problems, connective tissue disease, and neurologic symptoms.

13. DEVICE REPORTS - INAMED'S PRODUCT EXPERIENCE REPORT

Inamed provided a product experience report, involving adverse experience history and complaint data. The table below provides the number of complaints and the corresponding rates. Inamed considers the rates to be worst case because the numerator includes devices manufactured prior to 1991 but the denominator includes only sales after 1991. The complaint rates are provided as a percentage of total net sales.

Complication/Category	Complaints for all PMA Styles	Complaints for styles unknown	Total
Capsular contracture	3846	970	4816 [redacted]
Aesthetic complication/dissatisfaction	1833	240	2073 [redacted]
Rupture	917	547	1464 [redacted]
Surgical complication	904	211	1115 [redacted]
Infection/infection related	491	31	522 [redacted]
Malfunction	358	1	359 [redacted]
Autoimmune related	223	46	269 [redacted]
Cancer[1]	12	6	18 [redacted]
Death[2]	11	8	19 [redacted]
Decreased lactation[2]	2	-	2 [redacted]
Other[3]	1324	1141	1465 [redacted]

[1]All non-device related, except 1 patient with etiology unknown.
[2]All non-device related.
[3]Includes anxiety, asthma, bronchitis, calcification, cyst, pain, silicone migration, non-specific varied injuries.

[redacted]

14. LABELING - OVERVIEW

The labeling for this PMA consists of primary package labels, secondary package labels and documents, and patient brochure.

Primary Package Labels

The primary packaging consists of inner and outer thermoforms. The primary label is attached to the outer thermoform lid after sterilization. The primary label includes two patient record/device identification stickers that can be removed and affixed to the patient's device identification card and/or to the medical device registration form.

Secondary Package Labels and Documents

The secondary packaging consists of a 2-piece carton (lid and base), the primary package, and the documents packaged in the carton. The secondary packaging has two identical labels on opposite sides of the carton. The following documents are included in the secondary packaging:

- **Directions for Use (DFU) or package insert** - Along with the DFU provided in the package, the DFU will also be made available to the physician and patient at no charge from Inamed. It will also be available to view/print from the Inamed website.

- **ConfidencePlus™ McGhan® Breast Implant Limited Warranties Brochure** - This brochure describes Inamed's replacement and financial reimbursement policy. This brochure covers both McGhan saline and silicone implants. The standard ConfidencePlus™ warranty provides automatic enrollment with lifetime implant replacement and up to $1200 in financial assistance over a 10 year period. The optional Platinum program also provides 10 years of "guaranteed financial assistance," including up to $2400 out-of-pocket expenses for surgical fees, operating room, and anesthesia expenses not covered by insurance, contralateral implant replacement, and lifetime product replacement, for an enrollment fee of $100.

- **Patient's Device Identification Card** - This card is to be given to the patient to keep as a record of her breast implant device identification information. Additional copies of this document will be made available to physicians at no charge from Inamed. Note that stickers with product specific information are provided for quick completion of the card. To complete the Device Identification Card, one device identification sticker for each breast implant is placed on the back of the card. The stickers, which are attached to the primary package label, include the lot number, catalog number, and description of the device. If a sticker is not available, then the card should be completed by hand.

- **Medical Device Registration Form** - This form is to be used by physicians to register the device with Inamed. It is kept on file at Inamed. In addition, extra forms are available to the physician upon request and at no charge by Inamed. Note that stickers with product specific information are provided for quick completion of the card. The stickers, which attached to the primary package label, include the lot number, catalog number, and description of the device. If a sticker is not available, then the form should be completed by hand.

- **Patient Chart Labels** - Six (6) stickers to be used by physician/hospital staff to place device information in medical records/charts and other documents (e.g., insurance billing).

Patient Brochure – "Making an Informed Decision – Silicone-Filled Breast Implant"

The patient brochure is not distributed as part of the packaged device. Rather, it will be distributed to surgeons who will then provide it directly to their patients during consultation visits. The implementation plan for this brochure includes direct mailing copies to the Inamed surgeon customer list, along with a letter that describes the nature of the document and its intended purpose as part of the patient consultation and informed decision making process. The letter will

also include recommendations to make the brochure readily available in the surgeon office along with instruction on how to obtain additional copies, free of charge, from either the Inamed sales representative or from Inamed directly. Also, the patient brochure will be posted on Inamed's website (and FDA's). The patient brochure is the subject of the focus group study discussed below.

15. LABELING - FOCUS GROUP STUDY PROTOCOL

The overall purpose or goal of a focus group study is to improve the quality of the patient brochure. Inamed provided a draft focus group study protocol.

The individual objectives of the focus group study will be to understand:

- what questions and concerns women have when considering breast augmentation, breast reconstruction and breast implant revision
- to what degree the current literature addresses these questions
- what additional information should be provided
- if the language is understandable to the lay audience
- if the language is clear and well organized
- what, if any, improvements can be made to the current literature.

The focus groups will be conducted in person by an experienced professional contractor who will also summarize the results. Five in-person focus groups will be conducted (minimum 8 respondents per conference):

- Augmentation
  - 1 group with women who *have had breast augmentation*
  - 1 group with women who *have considered or are considering breast augmentation*
- Reconstruction
  - 1 group with women who *have had breast reconstruction*
  - 1 group with women who *have considered or are considering breast reconstruction*
- Revision
  - 1 group with women who *currently have breast implants and are considering or may have considered revision surgery to replace one or both of their implants*

The following questions will be asked of the focus groups:

- What did you think about the layout (format) of the brochure?
- What would you say are the main messages you got from reading this brochure?
- What new things did you learn from this brochure that you did not know before reading it?
- What did you like about this brochure?
- What did you dislike about this brochure? (Probe: anything offensive)

- What information will be most useful to you in helping you make an informed decision about whether or not to have silicone-filled breast implants? Not useful?
- What did you think about the illustrations in the brochure?
- What sections of the brochure or any terms used in the brochure did you find confusing or difficult to understand?
- What did you learn about the potential risks and benefits of breast implants?
- What did you learn from the clinical studies section (e.g., complication rates, additional surgical treatments, reasons for removals)? Explain how these clinical studies relate to you.
- What questions do you have about silicone-filled breast implants that this brochure did not answer?
- What additional comments or feedback do you have regarding this brochure, including suggestions for improving it?

After the contractor has provided Inamed with the report, Inamed will revise the patient brochure to reflect the appropriate changes and/or suggestions.

16. BIBLIOGRAPHY

The following are the references for this review memo.

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